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SYNTHESIS AND CHARACTERIZATION OF PHARMACEUTICALLY IMPORTANT CHIRAL INVERSION OF UNWANTED S ISOMER 3-(5-((S)-2-AMINOPROPYL)-7-CYANOINDOLIN-1-YL) PROPYL BENZOATE *VIA* 2, 4, 6-TRIPHENYLPYRIDINIUM SALT

Dr. Anil A. Ghanwat*, Bharat B. Kashid, Vithal M. Gugwad, Dnyanadeo J. Kesarkar

Chemistry Research Laboratory, School of Chemical Sciences, Solapur University, Solapur (MS), 413255, India.

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***Corresponding Author**
Dr. Anil A. Ghanwat
Chemistry Research Laboratory, School of Chemical Sciences, Solapur University, Solapur (MS), 413255, India.

ABSTRACT

Development of more effective method for inversion of the chiral centre of the unwanted isomer by optical resolution processes to increase the overall yield. The transformation is carried out in a three step synthesis via an SN2 type reaction of the 2, 4, 6-tri-arylpyridinium salt and a subsequent nucleophilic substitution by the azide ion, which on reduced by hydrogenolysis to give an Inversion degree of 85-100%. Low stereoselectivity caused by racemization to some extent was observed for the inversion of the optically active unwanted S isomer of amine 3-(5-((S)-2-aminopropyl)-7-cyanoindolin-1-yl) propyl benzoate **(Ia)**. However, modified reaction conditions allowed increased stereoselectivity, a more rapid and almost complete inversion of the chiral (S)-amine **(Ia)** to the chiral (R)-amine **(Ib)** of this substrate as well.

KEYWORDS: Pyrylium salts; Pyridinium salts; Azides; Inversion of configuration.

INTRODUCTION

Use of homochiral substances is rapidly increasing because of their importance in the pharmaceutical industry. It is essentials to develop the suitable methods and chiral synthesis for the preparation of pure enantiomers which is impressive. More profitable process is optical resolution can be obtained by increasing the overall yield after the inversion of chiral centre of 50% unwanted isomer to overcome the expensive racemic starting materials.

It is essential that synthetic transformations which involve such stereogenic centre proceed with complete stereoselectivity, either by full inversion of configuration or by retention of the

stereochemistry. For some substance groups there exist convenient chiral transformation methods based on nucleophilic substitution reactions for the preparation of compounds with new functionality or inversion, retention of configuration. In the recent years many new and creative applications of this reaction have been reported like amines to chiral alcohol[1-2] with opposite configurations using hydroxide, acetate or benzoate as nucleophiles. Nucleophilic attack on alcohols[3] and sulphonates[4-6] give inversion of configuration. As per reported methods shown the[7-8] at the stereochemistry of optically active amines can be completely inverted in a three-step synthesis.

It is evident from this recent literature summary that chiral transformations now are used over a broad synthetic spectrum. In contrast to the above mentioned groups, there are few known methods for the transformation of optically active amines to products with new functionality and specific stereochemistry. For that purpose there is a need for the development of stereoselective transformation reactions for amines. In our process the inversion was carried out with an SN2 type of reaction of the pyridinium compounds of amine by nucleophilic attack of the sodium azide ion. The azide product was reduced by hydrogenolysis to give the inverted amine.

MATERIALS AND METHODS

MATERIALS

All chemicals and solvents used were of synthetic grade unless otherwise noted. 3-(7-cyano-5-(2-nitropropyl)indolin-1-yl)propyl benzoate(1) purchased from MSN Laboratories Limited, ammonium formate, sodium bicarbonate were obtained from Sigma Aldrich, sodium azide, sodium iodide, Tartaric acid and sulfuric acid from Merck and, acetic acid and triethylamine were purchased from Acros organics. 2, 4, 6-riphenylpyrylium bisulphate was prepared as described method (US 4,150,233.1979, Example I A). Methanol, MDC, DMF, Ethyl acetate, Hexane and Acetone were used from Merck and DM Water from commercial source. Palladium carbon (10%; Type 390) from Johnson Matthey, Raney nickel (KALCAT 1961) from Monarch.

METHODS

1. Instrumentation

TLC: Merck TLC Silica Gel 60 F254, (0.25 mm) detection: UV light at 254 nm, CHIRAL HPLC: column: CHIRALPAK AD-H Polysaccharide-based chiral stationary phases (CSPs), Temp 25-30^{0}C, (250 mm x 4.60 mm x 5 µm), flow rate 0.8/mint., wavelength 225 λ, Diluent:

0.1% Diethyl amine in ethanol, Detector: *Waters 2487 Dual* λ Absorbance, ^{1}H NMR: Bruker Avance 400 MHz NMR Spectrometer, chemical shifts are reported in ppm downfield from TMS. Flash chromatography: Teledyne Isco Combiflash Rf+ Lumen (230-400 mesh), detector: ELSD, IR: Thermo Scientific Nicolet iS50 FT-IR Spectrometer and MS: Thermo Scientific LC-MS Orbitrap-based systems.

2. Synthesis of 2, 4, 6-Triphenylpyrylium Bisulfate[11] (II)

To a suspension of 223.04g (1.856 mmol) of acetophenone, mix well 134.0g (1.263 mmol) of benzaldehyde which is free of benzoic acid. Cool the mixture in an ice bath and added 200g of concentrated sulfuric acid in small portions with vigorous stirring. After the addition of acid is complete, place the flask in a boiling water bath and heat for approximately 6 hours and completion of reaction was confirmed by TLC (Hexane 9.5: Ethyl acetate 0.5). After heating, the reaction mixture is worked up by adding approximately 1200 ml of hot distilled water to the mixture in the flask. The organic layer is broken up with a stirring rod and the mixture is brought to a boil to dissolve the pyrylium bisulfate product. The aqueous solution of the pyrylium salt is then separated from the oily reaction byproduct by filtration through coarse filter paper. The aqueous phase is allowed to cool whereupon crystals of product separate. Yield of 2, 4, 6-triphenylpyrylium bisulfate (II) are generally between 139 -151g (27-29.5%). The product dried at 70° C without decomposition. NMR confirms the structure (II) Scheme II. $C_{23}H_{18}O_5S$, Elemental analysis: C: 67.97; H: 4.46; O:19.68; S:7.89, ^{1}H NMR 400 MHz, CDCl3: δ ppm: 2.78(S, 1H), 7.3-8.2 (m, 15 H), 8.62 (S, 2H), (^{13}C NMR 400 MHz, CDCl3: δ ppm:38.6, 38.8, 39.0, 39.3, 39.5, 39.7, 39.9, 114.4, 127.9, 127.9, 129.3, 129.4, 129.4, 131.7, 134.9, 134.9, 165.8, 169.9, :IR: ν(cm-^{1}), 618m, 679m, 772s, 872m, 996s, 1061s, 1167m, 1195m, 1250s, 1275m, 1470m, 1498s, 1593s, 1623s, 2609w, 2841w, 3070w and MP 270 ^{0} C.

3. Synthesis of Racemic 3-(5-((R/S)-2-aminopropyl)-7-cyanoindolin-1-yl) propyl benzoate[9-10] (A)

3-(7-cyano-5-(2-nitropropyl)indolin-1-yl)propyl benzoate (1) 25.0g (0.0634 mmol) charged in a autoclave reactor in methanol 250 ml ,ammonium formate 8.00g (0.127 mmol) and Raney Ni 8 % at room temp under nitrogen. Applied hydrogen pressure 10-12 bar at 40-45^{0} C for 16-18 hrs, completion of reaction was confirmed by TLC (MDC 9.5:0.5 Methanol), added water and extracted with ethyl acetate and evaporated solvent, gives the racemic mix of amine 22.0 g (A) had an optical(Chiral HPLC) purity of Ia = 51.26 % and Ib = 48.74 %.Scheme I.

4. Separation of Isomers and recovery of unwanted S isomer from mother liquor: (Ia)

The racemic mix of amine 22.0 g (A) with optical(chiral HPLC) purity 51.26:48.74 (Ia:Ib) was dissolved in acetone 61.6 ml and added slowly at 55-60^{0}C in L + tartaric acid 5.03 g (0.033 mmol) dissolved in water 16.5 ml then stir 25 hrs at room temp and filter to get the inverted R isomer of amine product 5-[(2R)-2-Aminopropyl]-1-[3-(benzoyloxy)propyl]-2,3-dihydro-1H-indole-7-carbonitrile (2R,3R)-2,3-dihydroxybutanedioate (Ib) had an optical (Chiral HPLC) purity of 1.53:98.47 ~ 85-100% (Ia:Ib) (10.88 g yield 35% (Ib)) Scheme I. The mother liquor containing unwanted isomer of amine treated with 20% aq.sodium bicarbonate solution in water and dichloro methane at room temp. Separated and Dichloro methane was evaporated to obtain the free base of unwanted S isomer had an optical (Chiral HPLC) purity of 90.73:9.27 ~80-90% (Ia:Ib) (14.2g) (Ia) was dissolved in acetone 40.0 ml and added slowly at 55-60^{0}C in D (-) tartaric acid 3.25g (0.0215 mmol) dissolved in water 10.7 ml then stir 25 hrs at room temp to get (Ia) had an optical (Chiral HPLC) purity of 94.58:5.42 (Ia:Ib) ~92-100% (9.5 g yield 29.5% (Ia). Scheme I.

5. Synthesis of 2, 4, 6-Triphenyl Pyridinium Bisulfate salt of 3-(5-((S)-2-aminopropyl)-7-cyanoindolin-1-yl) propyl benzoate[12-15] (III)

To a suspension of Tartaric acid salt of 3-(5-((S)-2-aminopropyl)-7-cyanoindolin-1-yl) propyl benzoate (Ia) 3.95g (0.0077 mmol) had chiral purity(94.58:5.42 (Ia:Ib) ~92-100%) and 2, 4, 6--triphenylpyrylium bisulfate (II) (3.0g (0.0077 mmol) in dichloro methane followed by addition of triethylamine (1.94g 0.0192 mmol) and the mixture was stirred at room temp. for 1 hr. Acetic acid (1.154 g, 0.0192 mmol) was added and the mixture was further stirred for 24 hrs at room temp. under nitrogen and completion of reaction was confirmed by TLC. (MDC 9.5:0.5 Methanol).Then charged DM water and pH was adjusted to neutral by using 20% sodium carbonate solution. Separated MDC layer was stripped off, and the crude product (5.72g, 99%) was purified by flash chromatography (gradient elution: Ethyl acetate 10%: 90% Hexane) to yield a Orange Crystalline pyridinium bisulphate (**III)** (4.1g, 70 %) Scheme II. $C_{45}H_{41}N_3O_6S$, Elemental analysis: C:71.88; H:5.50; N: 5.59; O:12.77; S:4.26, ^{1}H NMR 400 MHz, CDCl3: δ ppm: 1.28-1.30(d, 3H), 2.09-2.12(m, 2H), 2.09-2.9(m, 2H), 2.8-2.84(m, 2H), 3.53-3.58(t, 2H), 3.68-3.71(t, 2H), 4.42-4.43(t, 2H), 5.31(s, 1H), 6.31-6.37(s, 2H), 7.28-8.034 (m, 20 H), 8.037-8.055(s, 2H), ^{13}C NMR 400 MHz, CDCl3: δ ppm: 20.7, 27.0, 41.8, 44.9, 53.1, 62.4, 67.8, 87.4, 118.9, 124.8, 128.3, 128.4, 128.7, 129.6, 130.0, 131.1, 132.0, 133.0, 133.3, 133.8, 133.9, 152.0, 155.5, 166.6, IR: ν(cm^1) 704.05s, 763.27s, 889.5m,

1050.2s, 1213.6w, 1273.7w, 1314.39s, 1450.2w, 1598.7w, 1618s, 1712.58m, 2206.15m, 2952.92w, 3066.23w. MS [m/z (654.31 100%) positive mode]

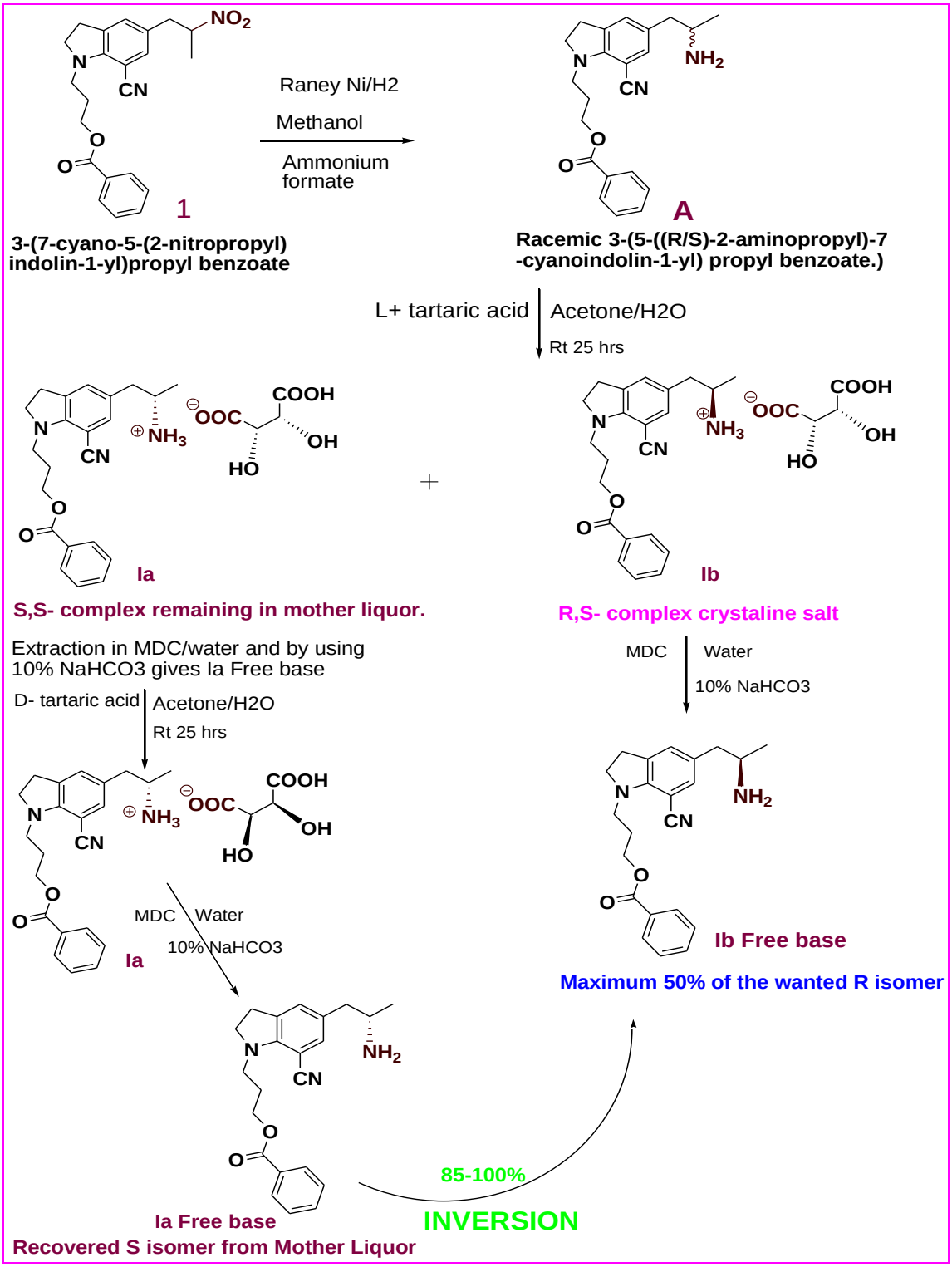
6. Synthesis of 3-(5-((R)-2-azidopropyl)-7-cyanoindolin-1-yl) propyl benzoate [7-8, 15] (IV)

2, 4, 6-Triphenyl Pyridinium Bisulfate salt of 3-(5-((S)-2-aminopropyl)-7-cyanoindolin-1-yl) propyl benzoate (III) 3g (0.0034 mmol) and catalytic amount of sodium iodide (0.5mg) was added in DMF (15 ml) followed by addition of sodium azide 1.04g (0.016 mmol) under nitrogen at room temp. Reaction mass was heated at 110-120^{0}C for 7-9 hrs. Checked TLC in (MDC 9.5: Methanol 0.5), cooled, charged water and extracted in ethyl acetate, evaporate the solvent. Purification of crude product was done by column chromatography afforded (1.44 g, 93 %) of (IV) orange oily mass Scheme II. $C_{22}H_{23}N_5O_2$, Elemental analysis: C: 67.85; H:5.95; N:17.98; O:8.22, ^{1}H NMR 400 MHz, CDCl3: δ ppm: 1.25-1.3(d, 3H), 2.15-2.21(m, 2H), 2.58-2.62(t, 2H), 2.97-3.01(d, 2H), 3.58-3.64(m, 3H), 3.76-3.8(t, 2H), 4.48-4.51(t, 2H), 6.98(s, 2H), 7.43-7.47(t, 2H), 7.55-7.59(t, 1H), 8.07-8.09(t, 2H), ^{13}C NMR 400 MHz, CDCl3: δ ppm:19, 27.1, 27.4, 29.7, 30.2, 31.4, 41.2, 45.2, 53.4, 58.9, 62.6, 87.9, 119.3, 126.3, 128.4, 129.6, 129.7, 130.1, 131.8, 132.7, 133, 151.9, 166.6, :IR: ν(cm^1), 674w, 711s, 893w, 963w, 1026m, 1070m, 1176m, 1270s, 1378w, 1451m, 1470m, 1580m, 1601m, 1716s, 2100s, 2208m, 2852w, 2927m, 2957m. MS [m/z (391.19 100%) positive mode]

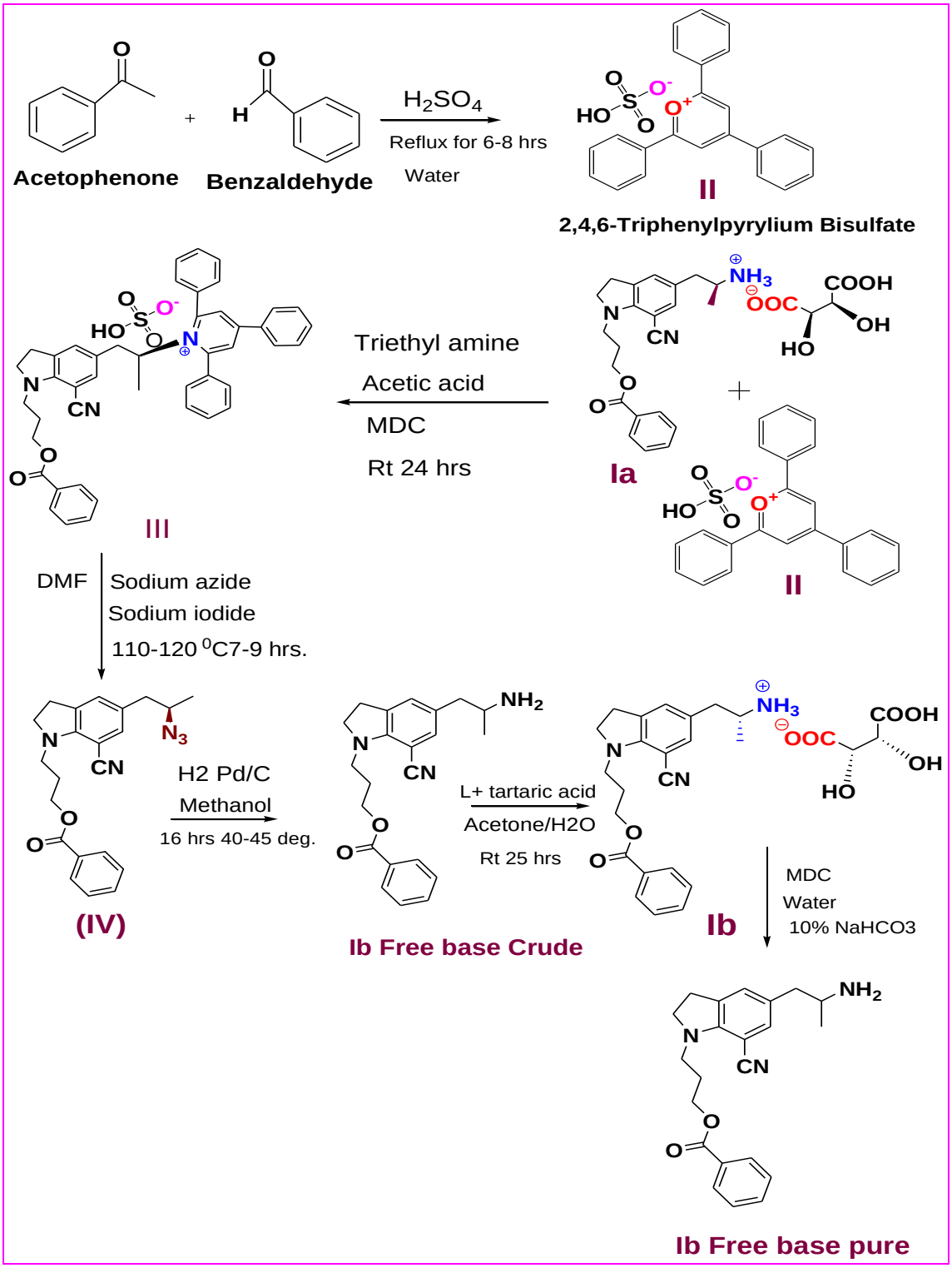
7. Synthesis of 3-(5-((R)-2-aminopropyl)-7-cyanoindolin-1-yl) propyl benzoate.[7-8] (Ib)

3-(5-((R)-2-azidopropyl)-7-cyanoindolin-1-yl) propyl benzoate (IV) 1.0g (0.0026 mmol) in methanol was hydrogenated over 12 % Palladium –on-charcoal for 16 hrs at 40-45 ^{0} C by using 5 bar hydrogen pressure and completion of reaction was confirmed by TLC (MDC 9.5:0.5 Methanol). The methanol was evaporated, crude product with optical(Chiral HPLC) purity (Ib: Ia 87.70:12.30) ~ 80-90% (Crude Yield 98% 0.915g) was dissolved in acetone 2.6 ml and added slowly at 55-60^{0}C in D+ tartaric acid 0.209g (0.00138 mmol) dissolved in water 0.75 ml then stir 25 hrs at room temp. to get the inverted R isomer of amine product 5-[(2R)-2-Aminopropyl]-1-[3-(benzoyloxy) propyl]-2, 3- dihydro-1H-indole-7-carbonitrile (2R, 3R)-2, 3-dihydroxybutanedioate (Ib), which on treated with 15% aq. Sodium bicarbonate solution in dichloro methane and water. Solvent was evaporated to obtain the inverted product had an optical (Chiral HPLC) purity of 1.53:98.47 (Ia: Ib) ~85-100% of (Ib free base) and yield (80% 0.75g) Scheme II. $C_{22}H_{25}N_3O_2$, Elemental analysis: C:72.70; H:6.93; N:11.56; O:8.80, ^{1}H NMR 400 MHz, CDCl3: δ ppm 1.09-1.11(d, 3H), 2.09-2.17(m, 4H), 2.38-2.52 (m, 2H), 2.93-2.97(t, 2H), 3.07-3.08(m, 1H), 3.56-3.6(t, 2H), 3.73-3.77(t, 2H), 4.45-4.48(t, 2H), 6.95-6.96(dd, 2H), 7.43-7.5(t, 2H), 7.57(t, 1H), 8.05-8.07(s, 2H), ^{13}C NMR 400 MHz, CDCl3: δ ppm:23.1, 27.1, 27.4, 44.9, 45.2, 48.4, 53.4, 62.6, 87.9, 119.5, 128.1, 128.3, 129.6, 129.7, 130.1, 131.5, 132.7, 133,

151.7, 166.6, IR: ν(cm-^{1}),711s, 732s, 815m, 882m, 1026m, 1070m, 1115s, 1212m, 1266s, 1314w, 1451m, 1579m, 1601m, 1715s, 2208m, 2928m, 2960m, 3055w, 3648w.MS [m/z (364.20 100%) positive mode].



Scheme 5A.1: Schematic representation of separation of Isomers and recovery of unwanted S isomer and inversion of 50% loss of unwanted S isomer into wanted R isomer (3-(5-((R)-2-aminopropyl)-7-cyanoindolin-1-yl) propyl benzoate).



Scheme 5A.2 Schematic representation of Inversion of unwanted S isomer into R isomer.

RESULTS AND DISCUSSION

The good leaving group ability of -NH2 can be greatly improved by converting the primary amine to the pyrilidium group[15], the pyrilidium group has been successfully replaced by a number of nucleophiles without concern of the stereochemistry.[15-17] It is reported that

nucleophilic attack by the azide ion gives inversion of configuration of sulfonates[5-6]. Azides can be reduced to amines by a number of methods[7-8]. The previously reported preliminary results for the inversion of (R)-1-methyl-3- phenyl amine (la)[8] showing that this optically active amine can be completely inverted in a three step synthesis .The inversion is carried out with an SN_2 type reaction of the pyridinium salt by nucleophilic attack of the azide ion[15-17]. The azide product is reduced by hydrogenolysis. In our process isolation of the Unwanted S isomer (Ia) from mother liquor and the inversion of unwanted S isomer to R isomer *via* 2, 4, 6-triphenylpyridinium salt with an SN_2 type reaction by nucleophilic attack of the azide ion. The azide product is reduced by hydrogenolysis to give the desired R Isomer of amine (Ib). Separation of Isomers and recovery of unwanted S isomer from mother liquor (Ia) was disclosed under experimental section (4).

Inversion of amino compounds *via* 2, 4, 6-triphenylpyridinium salts

The first attempt in the effort to invert the unwanted S isomer (Ia) to R isomer of amine (Ib) is the use of 2, 4, 6-triphenylpyridinium bisulphate (II).The compounds are known to be valuable intermediates in nucleophilic substitution of primary and secondary amines[18-19] (Katritzky *et al* 1979, Katritzky *et al* 1983), Which was reported their use in inversion of chiral amines (Said and Fiksdahl 2001b). Triphenylpyridinium salts are thermally stable and very reactive towards various nucleophiles. Intermediate 2, 4, 6-triphenylpyridinium salt (III) (scheme II) was prepared from 2, 4, 6- triphenylpyrylium bisulphate (III) and Tartaric acid salt of 3-(5-((S)-2-aminopropyl)-7-cyanoindolin-1-yl) propyl benzoate (Ia) (Scheme II) in 99% yield. The reaction was catalyzed by excess use of acetic acid and triethylamine to deprotonate the substrate, tartaric acid salt of 3-(5-((S)-2-aminopropyl)-7-cyanoindolin-1-yl) propyl benzoate (Ia) before it could attack the 2, 4, 6- triphenylpyrylium cation (II) (Scheme II). The nucleophilic displacement of compound (III) by sodium azide afforded high yields of the azide substitution product (IV). However, the stereoselectivity of the substitution reaction was satisfying; the products showed Chiral HPLC purity 85-100 % inversion (Table1).

"**Table 1.**"

Sr.No.	Product	Chiral purity	Yield
1	Isolated free base crude Ib: Ia	87.70:12.30	98%
2	Isolated tartarate salt pure Ib: Ia	98.47:1.53	80%
3	Isolated free base pure Ib: Ia	98.47:1.53	80%

Chiral HPLC: Inversion of unwanted S isomer into R isomer

In the present invention is a process for preparing the chiral inversion of optically active unwanted S isomer of amines (Ia) to R isomer of amines (Ib) with opposite configurations. The desired N-(aromatic) pyridinium[12-19] compounds of amine are prepared by reacting 2, 4, 6-Triphenylpyrylium Bisulfate[11] (II) precursor, with a primary amine having the desired aromatic substituent (Ia). Pyridinium compounds of amine (III) which on SN_2 type of reaction by nucleophilic attack of the sodium azide ion. The azide product (IV) was reduced by hydrogenolysis to give the desired inverted amine (Ib). The improved results (Ia) for the transformation and inversion of the pyrimidinium salt (III) to the azide (IV) thus include increased stereoselectivity and a drastic reduction of the reaction time. The modified reaction conditions for the azide nucleophilic substitution give nearly complete inversion of the chiral (S)-amine (Ia) 94% ee of the (S)-isomer to the (R)-amine (Ib) with (95-100% ee of the (R)-isomer. In conclusion, the use of the soft nucleophile sodium azide (7equiv.) in the polar aprotic solvent dimethylfomamide assisted by the addition catalytic quantity of sodium iodide represents an improved method for the nucleophilic substitution of pyridinium salt by the azide ion. These modified reaction conditions allow a more rapid and an almost complete inversion of the more easily racemized substrate, an optically active 5-[(2R)-2-Aminopropyl]-1-[3- benzoyloxy) propyl]-2, 3-dihydro-1H-indole-7-carbonitrile in a three-step synthesis. The nucleophilic substitution of pyridinium salt with azide represents a convenient method for inversion of configuration of the unwanted amine S isomer in optical resolution processes and can as such contribute to increase the overall yield in these processes to make them more efficient, profitable, economical, although no yield optimization was carried out.

CONCLUSION

The pyridinium compounds of amine are promising intermediates for the chiral inversion of optically active unwanted S isomer of amines to R isomer of amines with opposite configurations using sodium azide as nucleophiles 85-100 % inversion of configuration was obtained for the transformation of amine **(Ib).**

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