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Scalable approach for the synthesis of 5-fluro-6-subtituted indoles

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ABSTRACT

An efficient approach towards the synthesis of indoles, the heterocyclic core of many standard 5HT receptors agonists and pharmaceuticals used in many applications, *via* a modified Leimgruber-Batcho indole synthesis is presented. The process described herein is designed to suite the plant scale and is explained in multi kilogram quantities for 5-fluoro, 6-chloro indole, besides other substituted indoles that are reported with improved yields.

KEYWORDS

5-fluro indole leimgruber-batcho reaction;
Enamine;
Scalable process.

INTRODUCTION

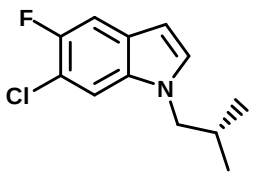
Indole is a heterocyclic nucleus which is a key constituent in a wide variety of pharmaceuticals with varied therapeutic applications and especially ones containing a fluorine group are used in dentistry, anesthesiology, hormone therapy, oncology, psychology, epilepsy, obesity[1], HIV inhibitors[2] and anti-malaria[3-10] etc.

An efficient method to synthesize indole core structure and its derivatives is warranted due to its importance in the pharmaceutical industry. Based on the literature leads, among the variously substituted indoles, synthesis of 6-substituted-5-fluoroindole core structure was desired as a synthetic target.

Many references are available in the literature about the indole synthesis *via* different named reactions and variety of methods[11-14].

The Leimgruber-Batcho reaction[15-16] continues to be a preferred one among the variety of known methods, new and old, to prepare substituted indole moiety and has become a popular alternative to the Fisher indole synthesis.

Here in, we report the synthesis of 5-fluoro-6-substituted indoles **(9-12)** using Leimgruber-Batcho reaction.



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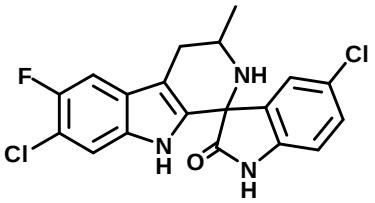

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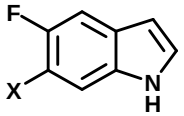
EXPERIMENTAL

NMR spectra were taken on a Varian 400 MHz, and chemical shifts are reported in parts per million (ppm) with the respective deuterated solvent peak as an internal standard. Mass spectra were recorded on



9 X=Cl
10 X=Br
11 X=I
12 X=NHAc

Figure 1 : Structures of targeted indoles to prepare

Agilent triple quadrupole mass spectrometer equipped with turbo ion spray interface at 375°C. Melting points were uncorrected, taken on Buchi B-540 Melting point apparatus. Reagents and solvents were obtained from commercial sources and used without further purification. All the purities were determined on HPLC X-Bridge shield RP18, 150×4.6, 4.6, 3.5µs column.

2-fluoro-4-methyl-5-nitroaniline (2)

Concentrated nitric acid (14Kg) was added drop wise to a stirred solution of 2-fluoro-4-methylaniline (25Kg) in concentrated sulphuric acid (125L) at -20°C in about three hours. The mixture was poured onto ice (1KL) and the pH adjusted between 9-10 using solid sodium hydroxide, maintaining internal temp below 50°C (observation: highly exothermic). After it attains room temperature, the solid was filtered. The wet cake was reslurried in water (100L) stirred and filtered to get a yellow solid. Mp: 80-82°C 32Kg. (92%). m/z: 171(M+1) ^{1}H-NMR: δ 2.49(3H,S), 3.88(1H, Br S), 6.91-6.94(1H, d), 7.49-7.51(1H, d).

3-chloro-4-fluoro-6-methylnitrobenzene (3)

A solution of sodium nitrite (4.46Kg) in water (11L) was added drop wise to a stirred suspension of 2-fluoro-4-methyl-5-nitroaniline (10Kg) in concentrated hydrochloric acid (120L).The mixture was stirred at 0°C for 30 min and then transferred to a dropping funnel and added drop wise to a stirred suspension of copper (I)chloride (9.31Kg) in concentrated hydrochloric acid (90L) at 0°C.The mixture was allowed to warm to room temperature and stirred for 4-6h, then poured onto ice water (150L). The isolated solid was filtered and dried at 50°C under vacuum. Off-white solid resulted. Mp: 59-60°C 7.2Kg. (67%). m/z: 187.8(M-1) ^{1}H-NMR: δ 2.62(3H, S), 7.13-7.16(1H, d), 8.14-8.17 (1H, d).

3-bromo-4-fluoro-6-methylnitrobenzene (4)

Same procedure as 3-chloro-4-fluoro-6-methylnitrobenzene except instead of copper chloride, HBr and copper bromide is used. A brown solid Mp: 61.5-63°C. (55%). ^{1}H-NMR: δ 2.62(3H, S), 7.13-7.16(1H, d), 8.14-8.17 (1H, d).

3-iodo-4-fluoro-6-methylnitrobenzene (5)

Same procedure as 3-chloro-4-fluoro-6-methylnitrobenzene exceptcopper iodide is used in lieu of copper chloride. A brown solid Mp: 46.5-47.5°C. (%Y=47%).^{1}H-NMR: δ 2.69(3H, S), 7.14-7.16(1H, d), 8.16-8.18 (1H, d).

3-hydroxy-4-fluoro-6-methylnitro benzene (6)

Same procedure as described for 3-chloro-4-fluoro-6-methylnitrobenzene except that hot water is used. A brown solid with Mp: 109-110°C (%yield 55%). m/z: 151.8 (M-F) ^{1}H-NMR: δ 2.52(3H, S), 6.56(1H, S), 8.39 (1H, S).

3-N-acetyl-4-fluoro-6-methylnitro benzene (7)

2-fluoro-4-methyl-5-nitroaniline (2, 10g) was dissolved in acetic anhydride (11.5ml, 2.5eq) and stirred for 30-min at room temperature (25-30°C) to get an off-white solid which was slurried in water, filtration followed by drying resulted in off-white solid, Mp: 172-173°C. (%Y 85) m/z: 212.9 ^{1}H-NMR: δ 2.25(3H, S), 2.55(3H, S), 7.04-7.07(1H, d), 7.402(1H, Br S), 9.0-9.05 (1H, d).

Preparation of 6-chloro-5-fluoroindole (8)

A mixture of 3-chloro-4-fluoro-6-methylnitro benzene (100Kg), N,N-dimethyl formamide di-isopropyl acetal (203.5Kg) and N,N-di methylformamide (400L) were heated to 100°c and stirred for 3hr. The mixture was cooled to room temperature and kept aside. A mixture of toluene (880L), acetic acid (800L), Iron powder (230Kg) and silica gel (200Kg) were heated to 60°c and stirred for 30min.To this mixture the above solution was added drop wise by maintaining the temperature below 80°C. The mixture was heated to 100°C and stirred for 2hr. Reaction progress was monitored by HPLC every hour. The reaction mixture was cooled to 50°C; ethyl acetate (1000L) was added and allowed to cool to room temperature (25-30°C). The mixture was then filtered, washed with ethyl acetate (2×1000L). The filtrate was washed with IN HCl (2×1000L), water (2×1000L) and with saturated bicarbonate (2×1000L) solution. The organic layer was dried over sodium sulphate (25Kg), concentrated in vaccuo to get crude, which was dissolved in (3:7) MDC and Hexane (1000L). Added silica gel (200Kg) and stirred for 20-30min, filtered and concentrated to get tan brown color solid with melting point (95-96°C). 64Kg. (72%). m/z: 167.7, 169.7; ^{1}H-NMR: δ 6.5 (1H, S), 8.12(1H, br S), 7.24-7.25(1H, d), 7.35-7.41 (2H, m).

6-bromo-5-fluoro indole (9)

Same procedure is used as for preparation of 6-chloro-5-fluoro indole, with starting material 3-bromo-4-fluoro-6-methylnitro benzene **(4)**. Mp: 81-83°C. (73%). m/z: 211.8, 213.8 (M-1) ^{1}H-NMR: δ 6.51(1H, S), 7.193(1H, m), , 7.34-7.37 (1H, d), 7.56-7.58 (1H, d), 8.13(1H, Br S).

6-iodo-5-fluoro-1H-indole (10)

Same procedure is used as for preparation of 6-chloro-5-fluoro indole, with starting material 3-Iodo-4-fluoro-6-methylnitro benzene **(5)**. Mp: 89-90°C. (70%). m/z: 259.8(M-1) ^{1}H-NMR: δ 6.51(1H, S), 7.22-7.25 (1H, M), 7.31-7.42 (1H, d), 7.55-7.57 (1H, d), 8.15(1H, Br s).

N-(5-fluoro-1H-indol-6-yl)acetamide (12)

Same procedure is used as for preparation of 6-chloro-5-fluoro indole, with starting material 3-N-acetyl-4-fluoro-6-methylnitro benzene **(7)**. Mp: 178-179°C. (70%). m/z: 192.9(M+1) ^{1}H-NMR: δ 2.25(3H, S), 6.47(1H, S), 7.46(1H, Br S), 7.55-7.57 (1H, d), 8.15(1H, Br S), 8.3 (1H, Br S), 8.43-8.46 (1H, d).

RESULTS AND DISCUSSION

Appropriately substituted nitrotoluene, starting material for the preparation of substituted indoles, compounds **(3-7)** are commercially unavailable and need to be synthesized. The synthetic route employed for the preparation of different nitrotoluenes is explained in scheme 1. Common precursor, 4-substitued-2-fluoro aniline **(1)** is nitrated yielding the corresponding nitro compound **(2)**. Diazotization, followed by Sandmeyer reaction using various copper salts[15] produced corresponding halo substituted nitrotoluenes **(3-7)**.

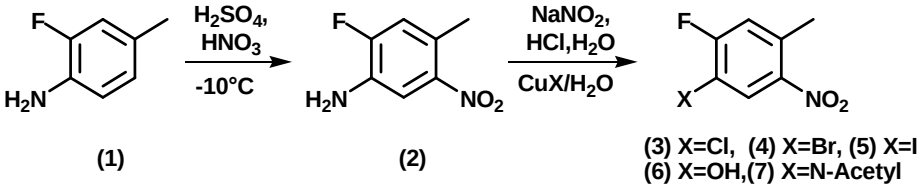
Bromo compound **(4)** has been selected for process development work and was treated with dimethylformamide-dimethyl acetal (DMF-DMA) to yield the corresponding enamine **(8a)**[16,17], that was reductively cyclised to the desired indole **(10)**.

While, preparing enamine **(8a)**, two important issues needed to be addressed. First one is the formation of methoxy impurity **(8b)** and second one is that methoxy formed almost in an equal ratio with the product. It was hypothesised and later proved that DMF-DMA, during the course of reaction, at high temperatures produces methanol as a by-product and this in-turn is responsible for the fluoro atom being replaced generating the coresponding Methoxy compound. The same observation was also evidenced in a research article[15]. Using instead dimethyl formamide diisopropylacetal (DMF-DIPA) resulted in much improved yields (>85-95%) with no trace of the fluoro displacement, probably due to the increased hindrance and less nucleophilic nature of isopropoxy anion.

Enamine **(8)** was reductively cyclised to yield respective indole (Scheme 2). Initially the yields of indole **(10)** achieved were only 40-45%. Scale up activity with these meager yields is not viable industrially. Moreover, most of the reported processes have used either hydrazine, Raney Ni or Pd/C as a reagent/catalyst of choice for reductive cyclisation in obtaining indole from corresponding nitro enamine (Scheme 3). However, most of our compounds contain halogen atoms in its structure rendering selection of Raney Ni or Pd/C unadvisable, besides being difficult to handle in bulk scale and use specialized equipments such as pressure reactors (autoclave) etc. These issues were targets for further optimization, while attempting to improve the process for reductive cyclisation to yield indole from respective enamine **(8)**. Searching through the available literature it was observed that iron has also been used as reducing agent in methanol/ethanol/ THF: water/acetic acid. Employing methanol/ethanol was not considered advisable anticipating methoxy/ ethoxy impurity. Even though, initial results with Fe/AcOH were promising, it needed lot of efforts to be reagent of choice. After examining various parameters, finally optimized condition that evolved was using Iron in AcOH/toluene at 100°C.

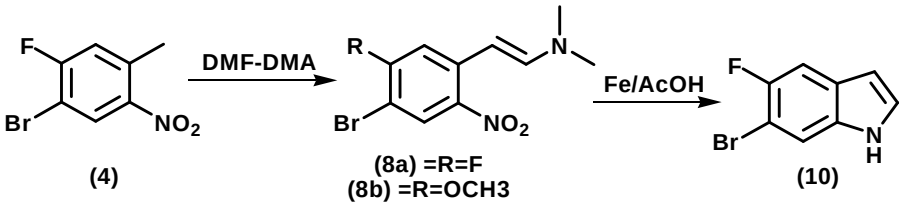
From flask to reactor: Obtaining an optimized process

Once feasibility of the above mentioned scheme was completed, process optimization was initiated to execute scale-up batches. The optimization work involves identifying acceptable ranges for parameters (temperature, pressure etc.), minimizing isolations & developing one pot process, minimization of solvent quantities used for reaction/extraction, material balance and others. These elements made the basis for us to improvement of the process accordingly.



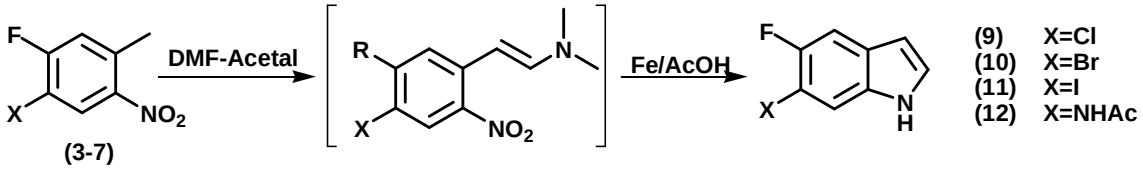
(1) (2) (3) X=Cl, (4) X=Br, (5) X=I
(6) X=OH,(7) X=N-Acetyl

Scheme 1 : Synthesis of 4-fluoro,3-halo (3-5) / Hydroxy (6), N-acetyl (7), nitrotoluenes



(4) (8a) =R=F (8b) =R=OCH3 (10)

Scheme 2 : Synthesis of 5-bromo-6-fluoro indoles



(3-7)

Scheme 3 : Synthesis of 5-fluoro, 6-substituted indoles

No operability issues or process criticalities were observed in the scheme 1, however in case of scheme 2, the biggest task was "preparation of DMF-DIPA", as it is not readily available in large quantities/ commercial lots. It was prepared by trans-acetalization using DMF-DMA and isopropanol[18,19]. By product methanol was removed by distillation through a short path column. The measured amount of collected methanol in receiver through distillation indicates progression and completion of the reaction. The product is characterized by ^{1}H NMR and Mass spectroscopy.

Amongst the technical tasks regarding the scale up of nitro toluene derivative with DMF-DIPA has been finding the optimum temperature of reaction. Most of the references have mentioned it to be 130-140°C. However, during the scale up, longer hours are needed to attain 130°C. To minimize the operational time & risk, various temperature ranges were screened and 95-105°C extent is identified as ideal to prepare enamine (Scheme 3). Lowering temperature of the reaction by about30°C resulted in decreased of operational time in plant execution by almost20%.

As a part of "What-if" studies, PAR-NAR (practical and normal acceptable range) studies, a reaction was conducted with nitrotoluene derivative and DMF-DIPA. We studied the observed instability of the formed enamine **(8)** in the reaction. HPLC purity of the enamine decreases as the reaction time increases Moreover it degrades into various minor impurities and each individual's % of area by HPLC is NMT (not more than) 5.0%. The enamine compound **(8)** was not stable for more than a week even at low temperatures. The instability of the enamine inspired us to think about carryng reaction without any hold ups all the way from substituted nitro toluene to enamine to amine and its subsequent cyclisation to obtain corresponding indole. After numerous attempts, optimized condition for the preparation of enamine and simultaneously activation of Fe in ACOH & toluene on silica gel at 60-70°C, emerged followed by addition of enamine reaction mixture to above activated iron yielded the targeted substituted indole. Addition of silica gel while activating iron, improved the stirring ability of the reaction followed by filtration gave the improved yields. This infact avoided use of column chromatography or silica/celite pulg. By incorporating 2N aq. HCl treatment away few of the impurities such as uncyclised amine, by-product dimethyl amine and improved the purity of the final product to 99% (by HPLC) from ealier crude 95% (by HPLC).

The universality of the process has been demonstrated on variously 6-substituted 5-fluro indoles, except that the reductive cyclisation didn't work for hydroxy nitro toluene **(6)**.

Here in this communication, total process of sub-

stituted indoles is explored and explained as an industrial feasible process in multi kilogram scale (executed in 25-100Kg scale). The synthetic scheme 2 is used in the complete study.

CONCLUSIONS

Three iterations of the development cycle were conducted, yielding substantial improvements in product quality, process safety, and productivity. A single stage indole process was explored and executed on 100Kg scale for 5-fluoro, 6-chloro, nitro toluene, affording a 70-75% yield and the process involves no tedious work ups and column chromatography, required for plant scale execution.

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