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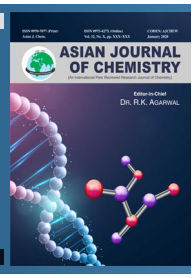

Novel Commercial Scale Synthetic Approach for 5-Cyanoindole: A Potential Intermediate for Vilazodone Hydrochloride, an Antidepressant Drug

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Present work describes the synthesis of 5-cyanoindole, a common intermediate used in various synthetic route of the antidepressant vilazodone hydrochloride. The protocol is both robust and commercially viable, utilizing readily available and low-cost materials and the isomers are environmental friendly than previously reported routes through its evading use of cyanide reagents and heavy metals.

Keywords: 5-Cyanoindole, Vilazodone hydrochloride, Ring closer reaction.

INTRODUCTION

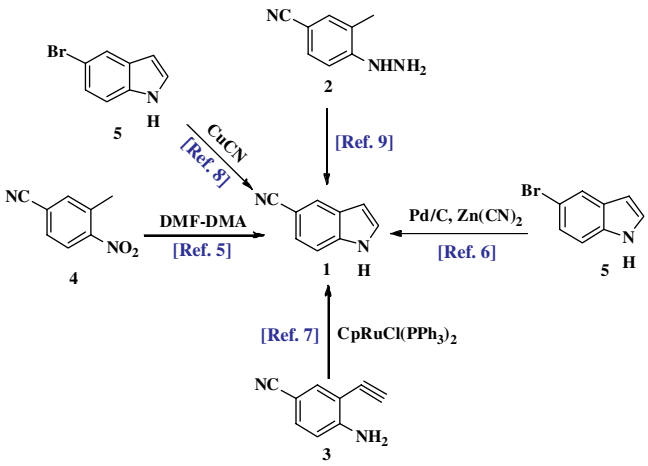
Heterocyclic compounds play a pivotal role in chemistry due to their prevalence in natural and synthetic drug scaffolds with significant pharmacological activity [1-3]. In particular, the wide range of applications of substituted indole motifs has drawn considerable attention due to their remarkable properties and prevalence in natural products. However, formation of substituted indoles presents a significant challenge on commercial scale due to the use of harsh conditions, toxic reagents and non-trivial starting materials. Many synthetic routes have been reported for the synthesis of the indole ring such as the classical Fisher-Indole synthesis [4], Leimgruber-Batcho indole synthesis [5], various transition-metal-catalyzed syntheses and multisteps one-pot synthesis [6-8] **(Scheme-I)**.

A key starting material for synthesis of vilazodone hydrochloride is 5-cyanoindole (**1**) [9]. The present industrial and commercial scale synthesis of 5-cyanoindole (**1**) involves conversion from 5-bromoindole (**5**) *via* various synthetic methods that typically employ toxic chemicals such as CuCN, $Zn(CN)_2$ and NaCN [6-8]. Because of this, conversion of 5-bromoindole (**5**) to 5-cyanoindole (**1**) is a tedious process and not recommended due to economical and environmental factors [10].

In this work, a systematic and robust process for the synthesis of 5-cyanoindole (**1**) by using inexpensive staring material 3-methyl-4-nitrobenzoic acid (**6**), which was converted to 3-methyl-4-nitrobenzonitrile (**4**) [11]. From here ring closer reaction was developed by modifying of Leimgruber-Batcho protocol [5]. This approach is a robust, economically viable and environmental free synthetic path.

EXPERIMENTAL

Synthesis of 3-methyl-4-nitrobenzamide (7): 3-Methyl-4-nitrobenzoic acid (**6**) (9 Kg) was charged with thionyl chloride (18 L) and dimethyl formamide (90 mL). The mixture was heated to reflux and maintained for 3 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to below 25 ºC and aqueous NH_3 solution (90 L) was added. The mixture stirred at room temperature for 2 h. The precipitated solid was collected by filtration, washed with water (9.0 L) and dried at 50 ºC for 8 h to afford 3-methyl-4-nitrobenzamide (**7**) (8.2 Kg). m.p. 148-150 ºC. Yield (theor./obtained): 0.99/0.911 w/w (92%). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.51 (s, 3H), 7.62 (br, 1H), 7.84 (d, 1H, d, J = 8.2), 7.92 (s, 1H), 8.01 (d, 1H, J = 8.2), 8.19 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 19.79 (CH_3), 124.81 (CH), 126.69 (CH), 132.30 (CH),



Scheme-I: Previously reported synthetic methods for 5-cyanoindole

133.02 (C), 138.62 (C), 150.83 (C), 166.65 (C); ESI: *m/z* calcd. for $C_8H_9O_3N_2^+$: 181.0613; found 181.0665.

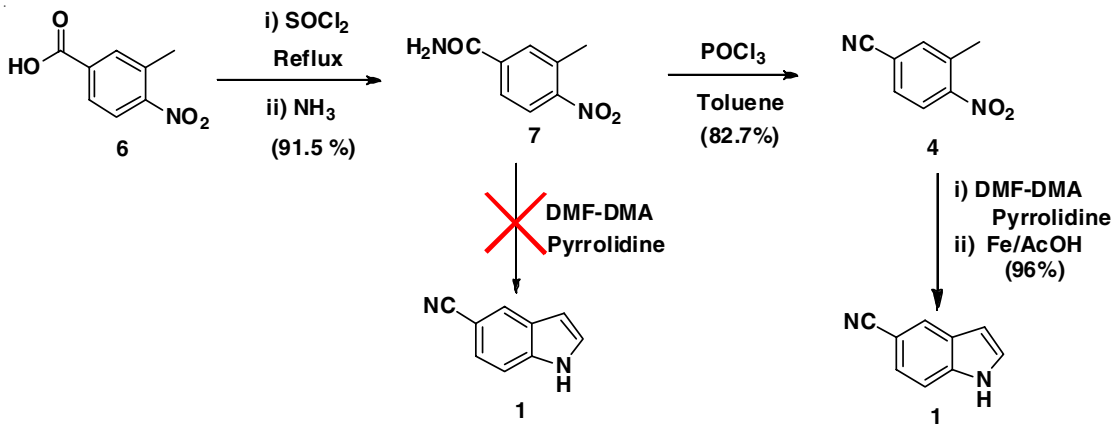
Synthesis of 3-methyl-4-nitrobenzonitrile (4): 3-Methyl-4-nitrobenzamide (**7**) (8.2 Kg) was dissolved in toluene (8.2 L) and thionyl chloride (8.2 L). The mixture was heated to reflux and maintained for 5-6 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to below 50 ºC and concentrated under reduced pressure. The resultant residue was dissolved in toluene (33 L) and washed with 5% sodium bicarbonate solution (2 × 8 L). The organic layer was concentrated, charged with hexane (18 L) and stirred at room temperature for 2-3 h. The precipitated solid was collected by filtration, washed with *n*-hexane (4 L) and dried at 50 ºC for 5 to 6 h to afford 3-methyl-4nitrobenzonitrile (**4**, 7.5 Kg). Yield (theor./obtained): 0.90/0.768 w/w (85.33%). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 8.10 (d, 1H, *J* = 8.5), 7.69-7.69 (m, 2H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm); 152.6, 137.6, 134.5, 130.6, 125.2, 117.0, 116.7, 20.0

Synthesis of 5-cyanoindole (1): 3-Methyl-4-nitrobenzonitrile **(4)** (6.3 Kg) was dissolved in methylene dichloride (14 L) and *N*,*N*-dimethylformamide dimethyl acetal (18 L). The mixture was heated to 50-55 ºC and maintained for 8 h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated under reduced pressure at below 50 ºC and charged with methanol (90 L) and acetic acid (61 L). The mixture was cooled to 0 ºC and added iron lot wise at 0 ºC, the reaction mixture heated again to 50-55 ºC for 8 h and the progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, filtered the reaction mass and washed with methanol (3 × 3 L). The organic layer was concentrated, charged with ethyl acetate (135 L) and stirred at room temperature for 3 h. The precipitated solid was collected by filtration, washed with *n*-hexane (13 L) and dried at 50 ºC for 6 h to afford 5-cyanoindole (**1**) (**Scheme-II**). Yield (theor./obtained): 0.0876/0.841 w/w (96%). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 8.67 (br, 1H), 7.99 (s, 1H), 7.50-7.40 (m, 2H), 7.36-7.32 (m, 1H), 6.67-6.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm); 137.59, 127.76, 126.58, 126.52, 124.97, 120.98, 112.12, 103.54, 102.88.

RESULTS AND DISCUSSION

The synthesis was initiated with commercially available, starting with low-cost material such as 3-methyl-4-nitrobenzoic acid (**6**) treated with thionyl chloride and catalytic amount of DMF (to improve the rate of the reaction) under reflux condition afforded the corresponding acid chloride, which was immediately converted to amide **7** by using aqueous NH_3 in good yield. The next following key challenging ring closer reaction was performed by Leimgruber-Batcho protocol. Unfortunately, this method was unsuccessful probably, the presence of free amide group cause the ring closed reaction (TLC showed multiple spots). To avoid this issue, amide **7** was converted into cyano functional group by dehydration method with $POCl_3$ under reflux condition to furnish compound **4** in good yield. The $POCl_3$ is an expensive chemical and not recommended for the industrials scale. However, thionyl chloride was used as dehydrating agent instead of $POCl_3$, which is a low-cost and commercially feasible for large scale synthesis. This generation of cyanide functionality **4** worked effectively by using thionyl chloride.

After successful synthesis of compound **4**, first ring closer reaction was attempted with DMF-DMA and stoichiometric ratio of pyrrolidine was used as an additive. The resulting reaction mixture was heated at 55 ºC furnished an uncyclized intermediate was isolated (not shown), which was reduced with $Na_2S_2O_4$ and MeOH at 50 ºC provided desired compound **1** in low yield (Table-1, entry-1) [5]. During the reaction, the reducing agent $Na_2S_2O_4$ was not completely dissolved in MeOH which



Scheme-II: Novel synthetic strategy for 5-cyanoindole

resulted in the poor yield. To overcome the solubility problem, reaction was performed with pre-dissolved reducing agent was used in combination of MeOH and water to obtained compound **1** in moderate yield. The little improvement has been observed (Table-1, entry-2). The next tuned by changing the different solvents, such as dioxane, THF with various combination of water (Table-1, entries-3, 4 and 5). However, did not observe any significant improvement in yield of 5-cyanoindole (**1**).

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS FOR RING CLOSER *via* MODIFICATION OF LEIMGRUBER-BATCHOS PROTOCOL

Entry	Solvent	Reducing agent	Temp. (°C)	Time (h)	Yield (%)
1	MeOH	$Na_2S_2O_4$	60	18	28
2	MeOH:AcOH	$Na_2S_2O_4$	60	6	21
3	MeOH:H_2O	$Na_2S_2O_4$	60	24	35
4	THF:$_2O$	$Na_2S_2O_4$	70	18	32
5	Dioxane:H_2O	$Na_2S_2O_4$	100	18	42
6	MeOH	Zn dust	60	5	63
7	MeOH:H_2O	Zn dust	60	8	68
8	AcOH	Zn dust	55	5	70
9	MeOH	N_2H_4 (Rani Ni catalyst)	60	8	65
10	MeOH	Fe (10 equiv)	0	18	73
11	MeOH	Fe (10 equiv)	0	24	65
12	MeOH	Fe (20 equiv)	0	12	69
13	MeOH	Fe (20 equiv)	0	9	75
14	AcOH	Fe (10 equiv)	0	3	83
15	AcOH	Fe (10 equiv)	RT	8	75
16	AcOH	Fe (10 equiv)	50	4	90
17	AcOH	Fe (10 equiv)	50	6	92
18	AcOH	Fe (5 equiv)	50	8	96
19	AcOH	Fe (5 equiv)	50	8	95
20	AcOH	Fe (5 equiv)	50	8	96
21	AcOH	Fe (5 equiv)	50	8	96

Now zinc metal was used as a better reducing agent as compared to $Na_2S_2O_4$. To study the zinc reactivity towards successful ring closer, the reactions were attempted with compound **4** with different stoichiometric ratios of Zn with MeOH and AcOH at various temperatures. This attempt could not achieve required percentage of the yield of 5-cyanoindole (**1**). The reactions with different reducing agents such as hydrazine hydrate and Raney nickel increases the yield of 5-cyanoindole (**1**) [5]. However, hydrazine hydrate and Raney nickel are expensive reagents and commercially not viable to synthesis of 5-cyanoindole (**1**).

To achieve the synthesis of 5-cyanoindole (**1**), our efforts were continued for an alternative and low cost reducing agent such as iron fillings. By using Fe, reaction was performed in MeOH as solvent at 50 ºC in 18 h observed complete consumption of the starting material and improvement of the yield for compound **1**. It was noted that the iron had a great influence on both the yield and the rate of the reaction (Table-1, entries 10). However, the reproducibility of the yield and reaction time were not consistent with these conditions (Table-1, entries 11-14). Hence, based on above preliminary experimental results, it is believed that Fe is the suitable reducing agent in all factors. Further evaluation of this reaction by tuning the solvent and temperatures effect in ring closer reaction.

After successfully identification of the suitable reducing agent, reactions were attempted in large scale with different stoichiometric ratio of iron and AcOH (Table-1, entries 14-17) [5,9]. During the addition of iron, highly exothermic has been observed and the reaction was completed in 1 h at room temperature (100 g scale reaction). It is also found that temperature also plays a factor to improve the yield of 5-cyanoindole. Reaction was tuned with lot wise addition of Fe at 0 ºC to room temperature for 8 h provided lower the yield (Table-1, entry 18). The addition of Fe at 0 ºC and raised the temperature at 50-55 ºC for 8 h obtained in an excellent yield. Finally, we have evaluated the best method for the ring closer reaction of compound **1**. Three batches in 5 kg level and same reaction conditions as (Table-1, entry -17) in lab scale synthesis were applied. The reproducibility of the yield was successfully achieved (Table-1, entry 19-21) in all the three batches.

Conclusion

In this work, various reducing agents were screened to develop a robust, economically viable and environmental free synthetic protocol for 5-cyanoindole. By utilizing this method, usage of toxic chemicals such as CuCN, $Zn(CN)_2$ and NaCN in the current industrial process can be avoided.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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