Efficient and Scalable Process for Synthesis of 5-Nitro-7- azaindole

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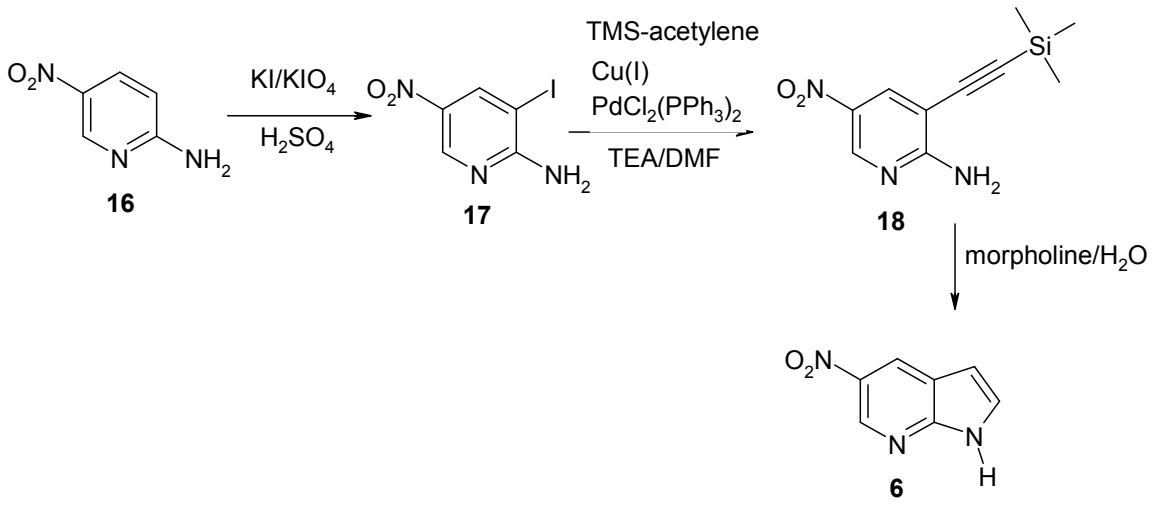
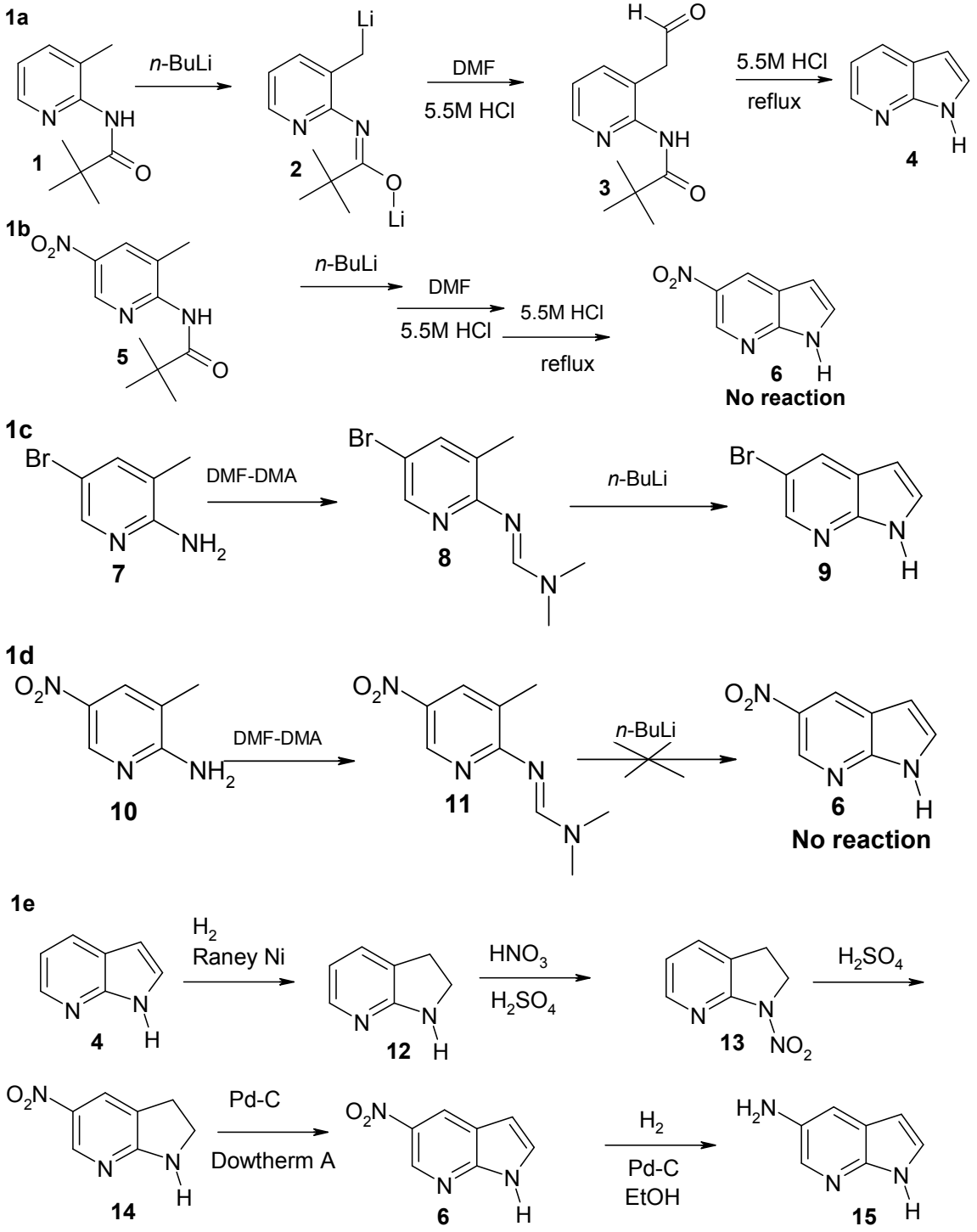

O2N
NH2
16
KI/KIO4
H2SO4
O2N
I
NH2
17
TMS-acetylene
Cu(I)
PdCl2(PPh3)2
TEA/DMF
O2N
Si
NH2
18
morpholine/H2O
O2N
N
N
H
6

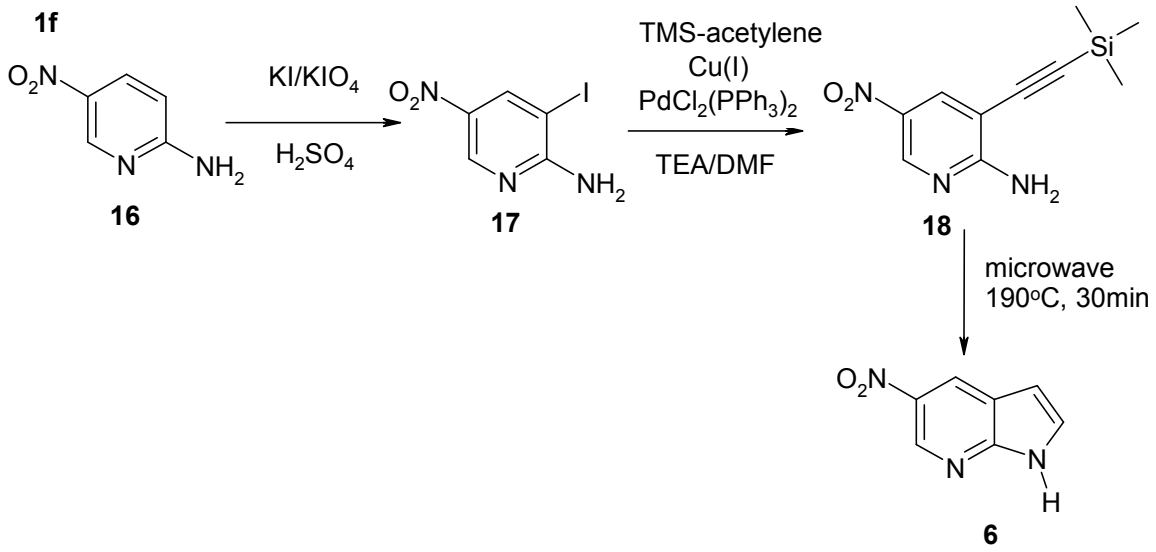
ABSTRACT: A simple and straightforward methodology for the synthesis of 5-nitro-7-azaindole **6** has been developed using metal free cycloisomerization of 5-nitro-3-trimethylsilanylethynyl-pyridin-2-ylamine **18**. Large-scale applicability of this newly developed method was successfully demonstrated on multikilogram scale to obtain 5-nitro-7-azaindole **6** in consistent yield and purity.

Keywords: Azaindole, trimethylsilylacetylene, morpholine, cycloisomerization.

INTRODUCTION

Azaindole constitutes one of the most important heterocyclic subunits in many pharmaceutically active compounds. Despite the usefulness in many drug candidates and molecules for various applications, no truly convenient process for its large-scale production has been published till day. The extensive use of azaindole intermediates in pharmaceutically active compounds has stimulated the synthetic developments for their synthesis. 5-Nitro-7-azaindole **6** is one of the key azaindole intermediate used for compound possessing anticancer activity.[1] Ready availability and cost of this key intermediate is a major concern. Not many reports are available in the literature for its synthesis. Frequently employed approach for azaindole synthesis begins with substituted pyridines which subsequently build a pyrrole ring to produce azaindole. However, electron-deficient nature of the pyridine ring influence the electronics of the π-system in such a way that many classical indole formation methods either do not work or result in poor yields when directly applied to the synthesis of azaindoles and its analogues. For example, ortho-lithiation of aniline and its derivatives is a versatile method for the synthesis of indoles. In particular, method developed by Hands et al[2] is a convenient method for the synthesis of 7-azaindole analogues. In this method 2-*tert*-butylcarbonylamino-3-methylpyridine **1** was dilithiated with *n*-BuLi at -60˚C to obtain dark red solution of lithiated dianion **2** which on quenching with DMF and HCl lead to 7-azaindole **4** in 81% yield (Scheme 1a). But the same strategy did not work for the synthesis of 5-nitro-7-azaindole **6** when 5-nitro-2-*tert*-butylcarbonylamino-3-methylpyridine **5** reacted with *n*-BuLi at -60˚C (Scheme 1b).


1a
n-BuLi
DMF
5.5M HCl
5.5M HCl
reflux
1
2
3
4
1b
n-BuLi
DMF
5.5M HCl
5.5M HCl
reflux
5
6
No reaction
1c
DMF-DMA
n-BuLi
7
8
9
1d
DMF-DMA
n-BuLi
10
11
6
No reaction
1e
H2
Raney Ni
HNO3
H2SO4
H2SO4
4
12
13
Pd-C
Dowtherm A
H2
Pd-C
EtOH
14
6
15



Scheme 1: Reported synthetic routes to 5-nitro-7-azaindole 6

Recently, simple cost effective synthesis of 5-halogenated azaindole **9** was reported by two step process without using heavy metal catalyst (Scheme 1c).[3] We attempted this method to synthesize 5-nitro-7-azaindole **6** using commercially available 3-methyl-5-nitro-pyridin-2-ylamine **10** in place of its 5-halogen analogue (Scheme 1d). 3-methyl-5-nitro-pyridin-2-ylamine **10** was converted to *N,N*-dimethyl-*N*'-(3-methyl-5-nitro-pyridin-2-yl)-formamidine **11** by reacting with dimethylformamide dimethylacetal in good yield.

However, cycloisomerization reaction on *N,N*-dimethyl-*N*'-(3-methyl-5-nitro-pyridin-2-yl)-formamidine **11** using similar conditions did not offer corresponding 5-nitro-7-azaindole **6**. We explored different bases such as lithium diisopropylamide, lithium bis(trimethylsilyl) amide, sodium bis(trimethylsilyl) amide, sodium methoxide for this cycloisomerization reaction. However, none of the bases afforded desired 5-nitro-7-azaindole **6**. It may be due to the presence of nitro group at 5-position on pyridine which alters the reactivity due to its electron withdrawing nature. Another reliable and general method for indole formation is Fischer cyclization. However, it often gives poor results

when pyridinyl hydrazines are used as substrates owing to the requirement of drastic reaction conditions.[1b, 1c] Other methods reported in the literature for the synthesis of 5-nitro-7-azaindole **6** suffer from various disadvantages and are not suitable for large-scale production. In 1959, Robison et al[4] reported first synthesis of 5-nitro-7- azaindole **6** using 7-azaindoline **12** (Scheme 1e) which was prepared by reduction of 7-azaindole **4**. In this procedure, 7-azaindoline **12** behaves like a substituted 2-aminopyridine which undergoes nitration reaction at 5-position of the pyridine ring without accompanying reaction at the 3-position. Nitration using a mixture of fuming HNO_3 and concentrated H_2SO_4 at -5°C first gives 1-nitro-7-azaindoline **13** which on treatment with concentrated H_2SO_4 gives desired 5-nitro-7-azaindoline **14**. 5-Nitro-7-azaindoline **14** on catalytic hydrogenation using Dowtherm offered 5-nitro-7-azaindole **6** in 21% overall yield. This process raises safety concerns and hence not suitable for large-scale production of 5-nitro-7-azaindole **6**. In recent times, reports on synthesis of 5-nitro-7-azaindole **6** mentioned microwave irradiation and metal mediated cycloisomerization reaction conditions.[5] Orthoaminohalo pyridines can be coupled with a terminal alkyne by Sonagashira reaction in high yields which on intramolecular cyclization gives required azaindole derivatives. Pearson et al[6] adopted this strategy and reported microwave assisted CuI catalysed synthesis of 5-amino-7-azaindole **6** in overall 66% yield and demonstrated its use up to 10 gm scale synthesis (Scheme 1f). However, isolation and purification of 5-nitro-7-azaiondole **6** was found to be problematic and 5-amino-7-azaindole **15** was isolated in 4 steps. We found this procedure promising for scale-up as it involved iodination of relatively inexpensive 2-amino-5-nitropyridine **16** followed by Sonogashira coupling of 3-iodo-5-nitro-pyridin-2-ylamine **17** with trimethylsilyl acetylene to get terminal alkyne which on

intramolecular cyclization provided required compound. In this context, to generate a large quantity of 5-nitro-7-azaindole **6** we decided to develop a robust process for its synthesis in multikilogram scale without performing chromatographic purifications.

ANTECEDENTS AND RESULTS

In the beginning, commercially available 2-amino-5-nitropyridine **16** was iodinated at 3-position using Batkowski procedure[7] to obtain 3-iodo-5-nitro-pyridin-2-ylamine **17** in 90% yields. During iodination reaction, it was observed that excessive evolution of iodine resulted in the condensation of iodine on condenser surface leading to complications in the reaction. To overcome this problem, we performed a few experiments by varying equivalents of KI and duration of KI addition. It was observed that evolution of iodine was comparatively less when 0.8 equivalent of KI was added dropwise for about 2 h. The reaction mixture was refluxed over 1h after KI addition to ensure complete consumption of the starting material. After the completion of the reaction, pH was adjusted to 7-8 by adding $NaHCO_3$ solution. The precipitated yellow solid was collected by filtration in excellent purity (>98% area by HPLC). After iodination reaction, next task that confronted us was to synthesize 5-nitro-3-trimethylsilanylethynyl-pyridin-2-ylamine **18** using Sonogashira coupling.[8] As per the reported method,[5] a mixture of 3-iodo-5-nitro-pyridin-2-ylamine **17**, triethyl amine (25.0 vol) in tetrahydrofuran (4.0 vol) and *N, N*-diethylacetamide (8.0 vol) was degassed for 30 min. Bis(triphenylphosphino) palladium(II) chloride (0.02 eq.) and copper (I) iodide (0.02 eq.) were added followed by the addition of trimethylsilylacetylene (1.5 eq.) in dropwise manner to obtain 5-nitro-3-trimethylsilanylethynyl-pyridin-2-ylamine **18** in 81% yield after column chromatography.

However, isolation and purification of the compound was problematic. To overcome this problem, we reacted 3-iodo-5-nitro-pyridin-2-ylamine **17** with trimethylsilylacetylene (1.2 eq.) in triethyl amine (4.0 vol) and DMF (1.0 vol) in the presence of bis(triphenylphosphino) palladium(II) chloride (0.02 eq.) and CuI (0.02 eq.) to get the required product by simple filtration in good yield. Encouraged by these results, we decided to optimize the molar equivalents of the catalysts bis(triphenylphosphino) palladium(II) chloride and copper(I) iodide to minimize the residual metal contamination in the product. Two different sets of the experiments were carried out at 5.0 g scale by varying amount of bis(triphenylphosphino) palladium(II) chloride from 0.001 to 0.02 equivalents and keeping amount of copper(I) iodide fixed to 0.02 equivalents. The results of these reactions are summarized in Table 1. It was found that the yield of the product was not affected at all when the equivalents of bis(triphenylphosphino) palladium(II) chloride was reduced to 0.002 (entries 1-6). However, further reduction in the molar equivalents resulted in the lower yield of the product even in 5 h stirring (entry 7). In the second set, same experiments were carried out by keeping the amount of bis(triphenylphosphino) palladium(II) chloride constant (0.002 equivalents) and varying the equivalents of copper(I) iodide from 0.006 to 0.02 equivalents. It is evident from the data summarized in Table 1 that Sonogashira coupling reaction offered compound 5-nitro-3-trimethylsilanylethynyl-pyridin-2-ylamine **18** in 89% yield after 3 h of reaction using catalysts bis(triphenylphosphino) palladium(II) chloride and copper(I) iodide in 0.002:0.008 molar ratio. It is noteworthy to mention here that the precipitated compound 5-nitro-3-trimethylsilanylethynyl-pyridin-2-ylamine **18** is readily isolated by filtration.

This optimized method yielded product 5-nitro-3-trimethylsilanylethynyl-pyridin-2-ylamine **18** in excellent yield with high purity (>98 % area by HPLC).

Table 1: Results of Sonogashira reaction carried out at different concentration of $Pd(PPh_3)_2Cl_2$ and CuI

Entry	$Pd(PPh_3)_2Cl_2$[b]	CuI	Time	Yield(%)[a]
Sonogashira coupling using different molar equivalents of $Pd(PPh_3)_2Cl_2$				
1	0.02	0.02	3	85
2	0.01	0.02	3	84
3	0.008	0.02	3	85
4	0.006	0.02	3	87
5	0.004	0.02	3	86
6	0.002	0.02	3	84
7	0.001	0.02	5	68
Sonogashira coupling using different molar equivalents of CuI				
8	0.002	0.02	3	86
9	0.002	0.01	3	87
10	0.002	0.008	3	89
11	0.002	0.006	4	65
12	0.002	0.008	2	74
13	0.002	0.008	4	88

[a] Isolated yield.

[b] We have tested only palladium catalyst bis(triphenylphosphino) palladium(II) chloride.

After successfully optimizing first two steps, the main obstacle was to carry out cycloisomerization reaction to get final compound **6**. Going through various cycloisomerization reactions reported in the literature, it occurred to us that the cycloisomerization reaction should be possible under basic conditions other than reported microwave irradiation. As a first attempt, we initiated cycloisomerization reaction trials of acetylene derivative **18** using catalytic copper (I) iodide in DMF, without using basic reagent. But these trials failed to give the required product. Under this cycloisomerization

reaction conditions mainly desilylated compound was isolated. After failing to cyclize compound **18** using Cu(I) in DMF, we carried out further cycloisomerization reaction trials using various bases and results are summarized in Table 2. When we attempted reaction using weak inorganic bases like $NaHCO_3$, K_2CO_3 (entry 4 and 6) and organic bases like triethylamine (entry 1, 2 and 3) could not activate the cyclization reaction whereas with strong bases like potassium *tert*-butoxide in *tert*-butyl alcohol we were able to get required compound 5-nitro-7-azaindole **6** in 50% yield. Similar reaction using 1M tetra-*n*-butyl ammonium fluoride (TBAF) in THF at 80°C afford required product in 52% yield after 24h (entry 8). However, the quality and purity of the obtained product **6** was not good and required column chromatography for its purification. Reactions using hindered base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene afford the required product in 57% yield (Table 2) (entry 7). On the other hand, reaction using organic bases like pyrrolidine, morpholine gave the required product with 60% and 65% yields, respectively (entry 9 and 10).

Table 2: Results of cyclization reactions carried out using different bases

Entry	Base	Solvent	Time (h)	Temp (˚C)	Yield(%)[a]
1	Et_3N	toluene	24	110	No reaction
2	Et_3N	THF	24	65	No reaction
3	Et_3N	MeCN	24	80	No reaction
4	K_2CO_3	toluene	24	110	No reaction
5	^{t}BuOK	^{t}BuOH	24	80	50
6	$NaHCO_3$	toluene	24	90	No reaction
7	DBU	toluene	24	110	57
8	TBAF	THF	24	65	52
9	pyrrolidine	pyrrolidine	24	90	60
10	morpholine	pyrrolidine	24	90	65

[a] Isolated yield.

Moderate-to-good yields were achieved for a variety of bases like DBU, pyrrolidine, morpholine. However, the methodology presented clear limitations especially in terms of applicability. After significant efforts, it appeared that a further improvement of these conditions was not straightforward. To develop a more general method suitable for large-scale synthesis we tried to find some solvent if that added to pyrrolidine or morpholine, could help the cyclization and enhance the interaction of the substrates. In our quest to develop scalable method, we carried out cycloisomerization reaction using pyrrolidine/water (1:1) molar ratio at 90°C over 24h and isolated required product in 67% yield. Similar reaction using morpholine/water (1:1) molar ratio at 90°C gave compound **6** in 73% yields after 24h. Among the different bases and solvents used for cyclization morpholine/water system emerged as the best of choice.

Before proceeding with large-scale synthetic efforts, we optimized the molar equivalents of the morpholine and water for optimal yield. Experiments were performed on 10.0 g scale at 90°C over 24h using different molar equivalents of the morpholine and water. The results of these experiments are presented in Table 3. Results showed that the yield of 5-nitro-7-azaindole **6** increased from 73% to 88% on increasing the molar equivalents of morpholine and water to 10:2 molar ratio (entry 6) further increase in molar equivalents of morpholine did not result in improvement of the yield beyond 88% (entry 6). It is noteworthy to mention here that 5-nitro-7-azaindole **6** was isolated from the reaction by filtration as yellow solid in high purity (> 97% area by HPLC). Using this synthetic route we were able to synthesize 5-nitro-7-azaindole **6** without using column chromatography and heavy metals for cycloisomerization. This improved synthetic protocol to produce 5-nitro-7-azaindole **6** was found to be superior to all other protocols

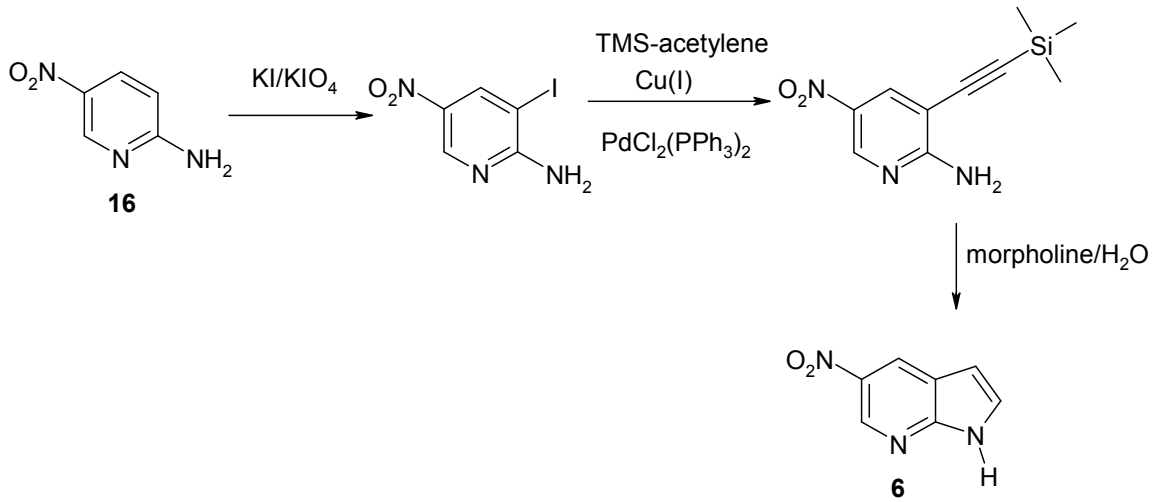
reported in the literature in terms of applicability and handling of the reaction conditions. However, we have not tried this synthetic route for the synthesis of substituted 5- or 6-azaindoles.

Table 3: Results of cyclization reaction carried out at different molar ratio of morpholine and water

Entry	Base/Solvent	Time (h)	Molar ratio	Yield(%)[a]
1	pyrrolidine/H_2O	24	1:1	67
2	morpholine/H_2O	24	1:1	73
3	morpholine/H_2O	24	6:4	75
4	morpholine/H_2O	24	7:3	79
5	morpholine/H_2O	24	8:2	85
6	morpholine/H_2O	24	10:2	88
7	morpholine/H_2O	24	10:3	88

[a] Isolated yield.

To validate the large-scale applicability of this improved synthesis of 5-nitro-7-azaindole **6,** all three synthetic steps were performed in triplicate on 1.0 kg scale (Scheme 2). The reaction progress was monitored by TLC and HPLC. The results of scale-up batches are presented in Table 4.



Scheme 2: An improved synthesis of 5-nitro-7-azaindole 6

Table 4: Results of scale-up batches

Entry	Batch size (kg)	Output (kg)	Yield(%)	HPLC purity[a] (%)
Step-1: Iodination				
1	1	1.70	89.47	98.40
2	1	1.68	88.42	98.10
3	1	1.71	90.00	98.05
Step-2: Sonogashira coupling				
4	1	0.779	87.01	98.03
5	1	0.774	88.32	98.12
6	1	0.765	86.93	98.00
Step-3:Cyclization				
7	1	0.610	88.01	97.81
8	1	0.608	87.80	97.67
9	1	0.609	87.90	97.89

[a] % area by HPLC

CONCLUSION

In conclusion, we have developed a simple and straightforward methodology for the synthesis of 5-nitro-7-azaindole **6**, which involves metal free cycloisomerization of 5-nitro-3-trimethylsilanylethynyl-pyridin-2-ylamine **18**. This method is safe, economical, easy to scale-up and the first of its kind for the synthesis 5-nitro-7-azaindole **6**. Large-scale applicability of this newly developed method successfully demonstrated by carrying out reactions on multikilogram scale to obtain 5-nitro-7-azaindole **6** in consistent yield and purity.

EXPERIMENTAL SECTION

All reagents and solvents were used as received. Starting materials were commercially available. Reactions were performed under anhydrous conditions unless noted otherwise. Reactions were followed by TLC analysis on Merck TLC aluminium sheets with silica gel 60 F254. The purities of compounds were assessed by analytical HPLC. LC/MS analysis was run on an Agilent 1200 MSD system with an Inertsil ODS-3V (250 *4.6

mm, 5 μm particle size). Chromatograms for electrospray ionization (ESI) positive and negative base peak intensity and a UV total absorption chromatogram from 220-300 nm were generated, and values for *m*/*z* are given; generally, only ions that indicate the parent mass are reported, and unless otherwise stated, the value quoted is $(M + H)^+$ for positive-ion mode and $(M - H)^-$ for negative-ion mode. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a 400 MHz (VARIAN AVANCE 400 AS) spectrometer. Chemical shift data for the proton and carbon resonances were reported in parts per million (δ) relative to internal standards $(CH_3)_4Si$ (δ 0.0). All coupling constants (*J*) are given in Hz. The purities of the final compounds were determined with Agilent 1200 HPLC system.

Preparation of 3-iodo-5-nitro-pyridin-2-amine 17: To a solution of 5-nitropyridin-2-amine **16** (1.0 kg, 7.1 mol) in H_2SO_4 (2M, 12L) was added potassium periodate (0.6 kg, 2.5 mol) portionwise (100 g lot in 5 min interval) at room temperature in 30 minutes. The reaction mixture was refluxed and aqueous potassium iodide (1.2 kg, 7.1 mol) was added dropwise over 2h. The reaction mixture was refluxed for 1.5h. Reaction mixture was cooled to room temperature and was neutralized by solid sodium bicarbonate. To the reaction mass sodium thiosulphate was added with stirring. Yellow colour solid separated out and was filtered dried to get 3-iodo-5-nitro-pyridin-2-amine **17** (1.68 kg, 88.42%). ^{1}HNMR (400MHz, DMSO-d_6): δ 7.15 (bs, 2H), 8.56 (d, J = 2.8 Hz, 1H), 8.84 (d, J = 2.8 Hz, 1H); MS (ESI): *m/z* = 266.1 $[M + H]^+$; HPLC purity : 98.8% area (254.0 nm).

Preparation of 5-nitro-3-(2-trimethylsilylethynyl) pyridin-2-amine 18: A mixture of 3-iodo-5-nitropyridin-2-amine **17** (1.0 kg, 3.7 mol), triethyl amine (4.0 L), *N, N*-dimethylformamide (1.0 L) was degassed for 30 minutes with nitrogen. Copper (I) iodide

(0.05 kg, 0.03 mol) and bis(triphenylphosphino) palladium(II) chloride (0.05 kg, 0.007 mol) was added to the reaction mass. The reaction mixture was stirred and trimethylsilylacetylene (0.43 kg, 4.4 mol) was added dropwise. The reaction mixture was stirred for 3h. Yellow colour solid separated out was filtered, washed with water (2.0 L) and dried to get 5-nitro-3-(2-trimethylsilylethynyl) pyridin-2-amine **18** (0.77 kg, 87.01%). ^{1}HNMR (400MHz, DMSO-d_6): δ 0.25 (s, 9 H), 7.15 (bs, 2H), 8.18 (d, J = 3.2 Hz, 1H), 8.85 (d, J = 2.4 Hz, 1H)); MS (ESI): m/z = 236.4 $[M + H]^+$; HPLC purity : 98.6 % area (254.0 nm).

Preparation of 5-nitro-7-azaindole 6: To a solution of 5-nitro-3-(2-trimethylsilylethynyl) pyridin-2-amine **18** (1.0 kg, 4.25 mol) in water (230 mL, 12.75 mol) was added morpholine (3.7 kg, 42.5 mol). The mixture was stirred at 90°C for 24h. Then the mixture was cooled to room temperature and diluted with water (2.0 L) and yellow colour solid was separated out was filtered, washed with water and dried to get 5-nitro-7-azaindole **6** (0.6 kg, 87.8%). ^{1}HNMR (400MHz, DMSO-d_6): δ 6.74 (d, J = 3.2 Hz, 1H), 7.71 (s, 1H), 8.88 (d, J = 2.4 Hz, 1H), 9.10 (d, J = 2.4 Hz, 1H), 12.49 (s, 1H); MS (ESI): m/z = 164.2 $[M + H]^+$; HPLC purity : 99.1 % area (254.0 nm).

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