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m-CPBA-$NH_{3(g)}$ system: A safe and scalable alternative for manufacture of (substituted)pyridine and quinoline N-oxides†

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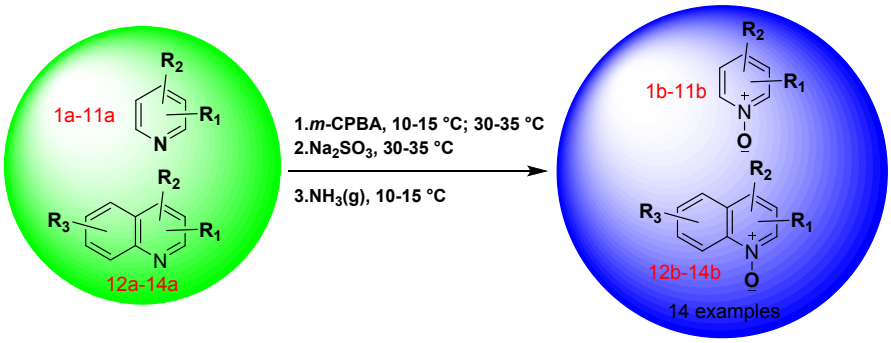
GRAPHICAL ABSTRACT:



ABSTRACT: An improved safe and scalable isolation process for (substituted) pyridine and quinoline *N*-oxide with quantitative yield along with high purity products using *m*-CPBA-$NH_{3(g)}$ system have been described. The safety was accessed by reaction calorimetry and DSC studies during conversion and isolation steps for possible hazards. The careful interpretation of the data substantiates the safety and scalability. The process flow is simplified to meet the industrial requirement of safety, cost-effectiveness, utility minimization. The reaction was safely demonstrated at 2.5 kg scale.

KEYWORDS: Pyridine, Pyridine *N*-Oxide, *m*-CPBA, Ammonia.

1. INTRODUCTION

In recent years, the importance of heterocyclic *N*-oxides is continuously growing in the field of research and industrial application. The *N*-oxide scaffold is an integral part of several drug molecules such as tirapazamine, an anticancer,[1] and pyrithione zinc as fungistatic and bacteriostatic.[2]They have also been a promising lead compound in the new drug discovery for HIV,[3] cancer,[4] tuberculosis[5,6] and type II Diabetes.[7]Moreover *N*-oxide derivatives of substituted pyridine serve as a key raw material for synthesis of rabeprazole and antiulcer,[8] lansoprazole, a proton pump inhibitor.[9] The 2- and 4-substituted pyridine and quinoline *N*-oxides have a high demand in drug development[10] and are synthesized by Polonovski rearrangement in presence of acetic anhydride[11] or trifluoroacetic acid.[12,13]

There are several reagents used for the *N*-oxidation of heterocycles like peracetic acid/AcOH,[14] perbenzoic acid,[15] monoperpthalic acid,[16] H_2O_2/AcOH,[17] H_2O_2/[Mn(TDCPP)Cl],[18] H_2O_2/MTO, BTSP/$HOReO_3$,[19,20] dimethyl dioxirane.[21] The aforesaid methods have restricted application at the industrial scale due to safety concerns like explosions[22] at elevated temperatures with the

decomposition of oxidant[23] and the product. Since *N*-oxides are highly water soluble, poses difficulty in isolation and purification during biphasic extractive workup. To scale up *N*-oxides manufacture to higher volumes, there arises a need for the development of a simplified process which meets the industrial requirement of safety, cost-effectiveness, minimizing utilities and waste.

Safety in the reactions at the manufacturing scale is of utmost importance. The reagent used and the products are of explosive nature hence necessitate the careful assessment of heat changes and stability of the chemicals involved at these conditions. The safety studies using reaction calorimeter and differential scanning calorimetry (DSC) for identifying the onset of degradation is very much required.

Herein, we report the industrial protocol for preparation of *N*-oxides of (substituted) pyridine and quinoline using an organic oxidant. Amongst the many oxidants reported for *N*-oxidation, *m*-CPBA was chosen to use under controlled conditions of solvent compatibility, mode of addition, the temperature along with scavenging of excess peroxides in the reaction mixture.[24,25]

2. RESULTS AND DISCUSSION

In all the initial experiments oxidation step showed the quantitative conversion, the only hurdle to be tackled was to separate *m*-chlorobenzoic acid generated during the reaction and *N*-oxides from the reaction mixture. The attempts were made to precipitate *m*-chlorobenzoic acid as a salt using organic and inorganic bases such as sodium bicarbonate and triethylamine. The salts being water soluble and insoluble in organic solvents, may be separated from the mixture either by extractive work up or filtration. Among the bases used, sodium salt resulted in poor yield due to the considerable water solubility of the product, while triethylammonium salt, did not precipitate

from the reaction solvent which was expected to be filtered. To overcome these complexities, one more alternative was attempted to convert *m*-chlorobenzoic acid into its ammonium salt not by aqueous liquor ammonia but by sparging anhydrous ammonia gas into the reaction mass in an organic solvent. To our surprise, ammonium *m*-chlorobenzoate precipitated from the reaction mixture, which was separated quantitatively by filtration on the Celite bed. Hence there was a necessity to optimize the aforesaid initial findings to achieve maximum recovery of *m*-chlorobenzoic acid and solvent.

2.1 Protocol Development

The experiments were planned to ascertain the effect of chlorinated, hydrocarbons and ester solvents (Table 1). Although the oxidation preceded smoothly in hexanes and cyclohexane but posed difficulties of non-filtrable cake of ammonium *m*-chlorobenzoate which entrapped the product (Table 1 entries 3 and 4). In addition to this, the hydrocarbon solvents are highly flammable even with an electrostatic charge. Use of dichloromethane (DCM) gave comparable yield with the reasonable recovery of solvent while dichloroethane (DCE) with similar results and better solvent recovery (Table 1 entries 1 and 2) suggested in the literature, that DCM would be a choice of solvent for oxidation purpose.[24] But there are certain issues at higher concentration of *m*-CPBA in DCM due to intrinsic instability of *m*-CPBA even though they are compatible.[26] However, the chlorinated solvents being ICH class 1 and 2 needs replacement to address the issues of toxicity, high volatility, and recovery. Hence, the use of environmentally benign ICH class 3 solvents such as ethyl acetate (EtOAc) and isopropyl acetate (iPrOAc) was desirable. Both the solvent gave comparable yield and purity of the desired product with better recovery, while isopropyl acetate was the solvent of choice (Table 1 entries 5 and 6). We also studied the compatibility of *m*-CPBA in iPrOAc in which the onset temperature was found to be 50.07 °C

which was much lower than the decomposition temperature of *m*-CPBA 89 °C in solid state and heat release of 205.3 J/g[26] (Fig 1). The temperature during the addition and quenching of m-CPBA is much lower that the onset temperature. Hence, this confirms that *m*-CPBA does not react or forms a hazardous combination with iPrOAc.

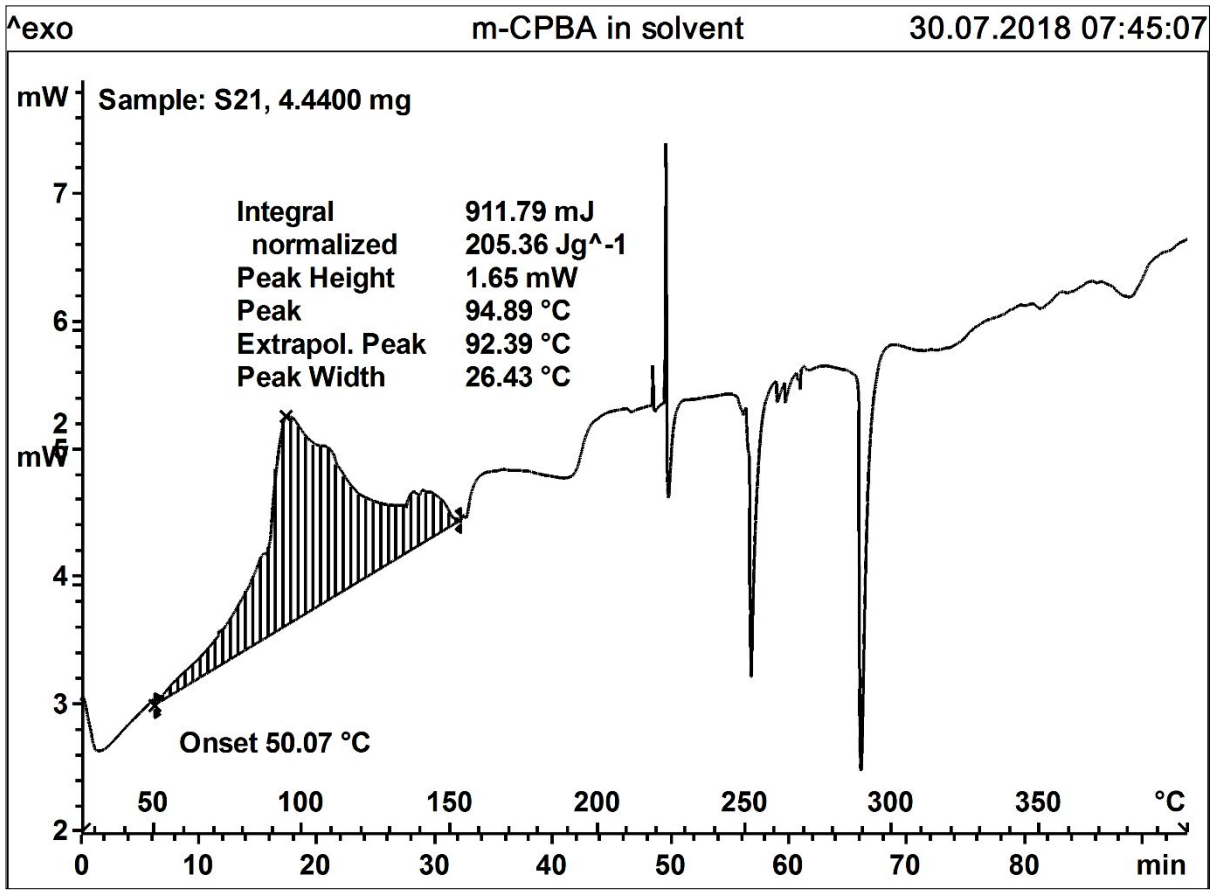


Fig 1. DSC graph (test range 30-400°C) of 0.3g/mL *m*-CPBA in iPrOAc.

Table 1. Solvent optimization and recovery study[a]

Entry	Solvent[b]	Class	Yield (%)[c]	Purity (%)[d]	Solvent Recovery (%)
1	DCE	1	90.0	95.0	85-90

2	DCM	2	89.0	95.6	55-60
3	Hexanes	2	98.0	99.0	62
4	Cyclohexane	2	98.1	99.2	60
5	EtOAc	3	98.0	96.0	82-85
6	iPrOAc	3	98.0	99.8	90-92

[a]Experimental condition: pyridine (200.0 g, 2.5316 mol 1.0 equiv.), [b]10 vol., 75% *m*-CPBA (610 g, 3.53 mol, 1.4 equiv.), [c]Isolated yield, [d]Isolated product purity by GC

The oxidation is known to be an exothermic reaction; to avoid the runaway necessitates the determination of heat of reaction using reaction calorimeter. Hence, initially, the temperature and time optimization studies were performed to access the ΔT both during the conversion and isolation steps (Table 2). As per the protocol of 200.0 g input batch of pyridine, the oxidant *m*-CPBA was added in 10 portions, maintaining the temperature of the reaction mass between 10-15 °C. The temperature was optimized during the addition of *m*-CPBA and the course the reaction till completion. The results revealed that it was necessary to maintain the temperature between 10-15 °C during the addition of *m*-CPBA, followed by maintaining it to 30-35 °C up to 4h, this resulted in maximum conversion as well as purity of the product accessed by GC. The aforesaid protocol was subjected to reaction calorimetric assessment using RC 1 (Mettler Toledo Inc.) to measure the heat of reaction, adiabatic temperature rise and Stoessel's criticality class (Fig 3a and b). The trends of heat changes indicated by RC 1 during the addition of *m*-CPBA are depicted in Fig 2.

Table 2. Time and temperature optimization study[a].

Entry	Temperature (°C)[b]	Time (h)[c]	% Conversion[d]
1	10-15	2	78.2
		4	82.3
		6	85.6
2	20-25	2	85.7
		4	88.7
		6	90.5
3	30-35	2	98.5
		4	98.5
		6	98.5

[a]Experimental condition: pyridine (200.0 g, 2.53 mol, 1.0 equiv.), iPrOAc (10 vol), 75% *m*-CPBA (610.0 g, 3.53 mol, 1.40 equiv.). [b]During addition of *m*-CPBA. [c]After addition of *m*-CPBA. [d]by GC

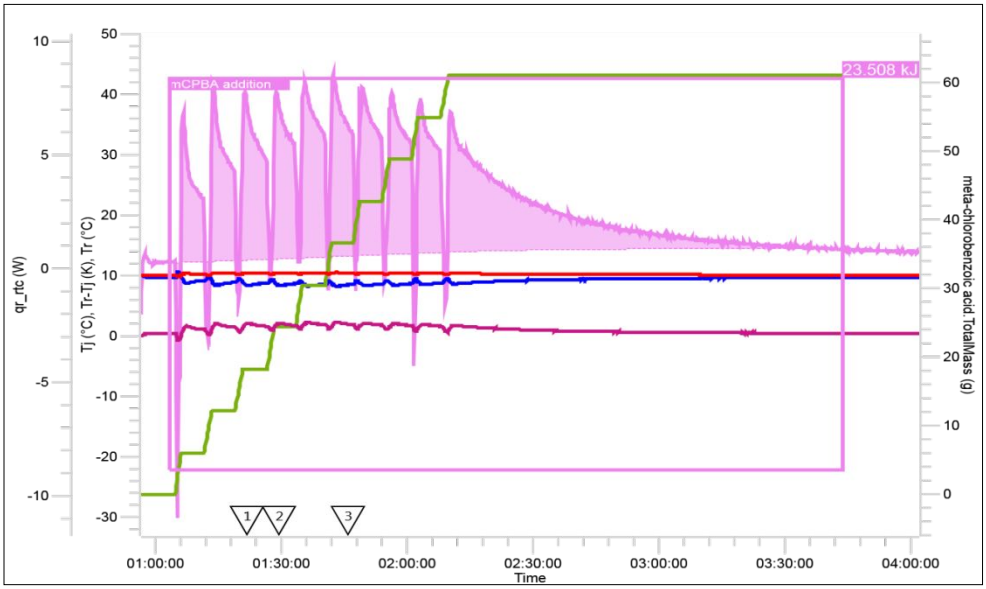
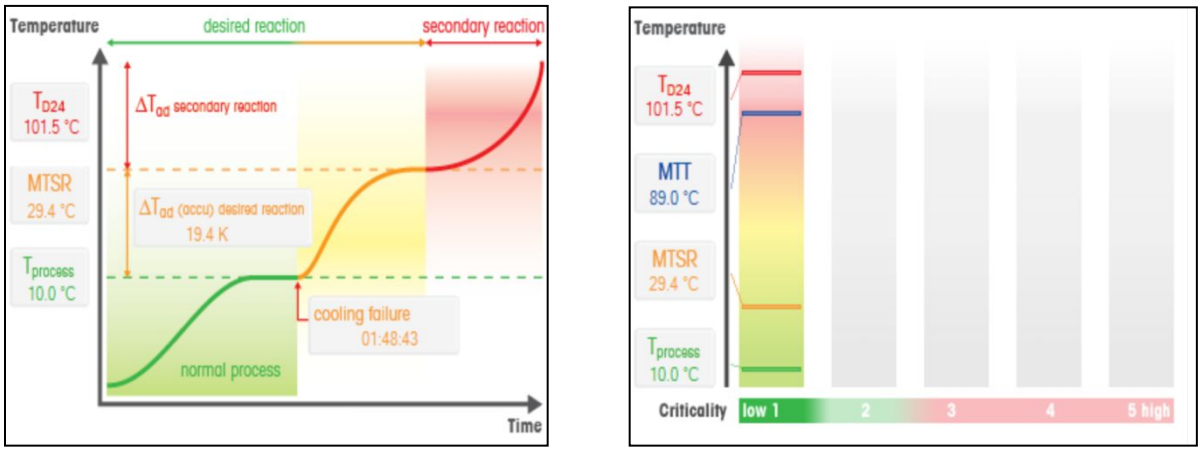


Fig 2. RC1 trend of *m*-CPBA addition (--- Tr; --- Tj; --- qr_rtc; ---Vr; ---Tr-Tj; ---Rt)

As depicted in Fig 2 and 3 the maximum heat rise during the addition of 10 portions of *m*-CPBA was 19.4 K with Maximum Temperature of Synthetic Reaction (MTSR) 29.44 °C and Onset of Decomposition Temperature (TD_{24}) 101.5 °C calculated by extrapolation using n^{th} order kinetic software w.r.t DSC data of reaction mixture, indicating that the reaction is safer even if the cooling fails, as MTSR is much lower TD_{24} limit. The Stoessel's criticality class is 1for *m*-CPBA addition operation, which is regarded as safe (Fig 3).[27]



(a) (b)

Fig 3. (a) Runaway Graph Based on Current Values of *m*-CPBA addition. (b) Stoessel's criticality class for *m*-CPBA Addition.

2.2 Quenching of excess oxidant and work up procedure:

The oxidation reaction was performed with 1.4 equivalent of commercially available *m*-CPBA (75% w/w). There is a possibility of traces of peroxide present at the end of reaction time which may lead to an explosion. To design hazards-free workup procedure necessitates quenching of unreacted *m*-CPBA with suitable scavenger prior to ammonia sparging and evaporation of the solvent. To accomplish this sodium sulfite, a cost-effective scavenger with no product contamination was used. Sodium sulfite was added at the completion of the reaction until the test was negative on MN-Quantofix strip. No heat change was observed during the addition of

sodium sulfite. This was followed by sparging anhydrous ammonia gas to convert *m*-chlorobenzoic acid into ammonium *m*-chlorobenzoate. Formation of the ammonium salt is an exothermic process hence needs to be performed at a lower temperature with control on the amount and rate of ammonia gas sparging. The rate of gas sparging was optimized to 180-200 mL/min. while maintaining the reaction temperature between 10-15 °C, till the reaction mixture pH raised to 8-9. This neutralization protocol was studied using reaction calorimeter, RC 1 to establish the safe handling temperature of a reaction mixture containing explosive *N*-oxide. The RC1 trend of ammonia sparging is depicted in Fig 4.

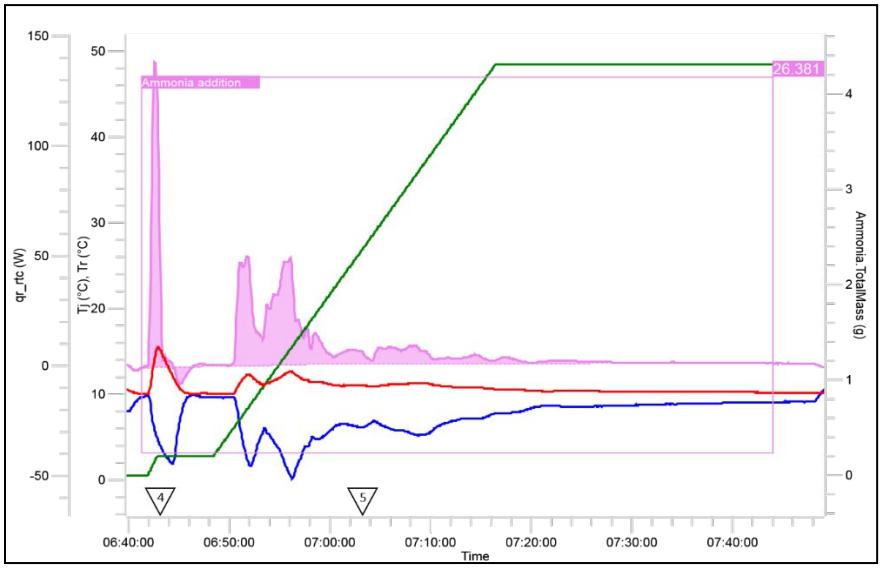
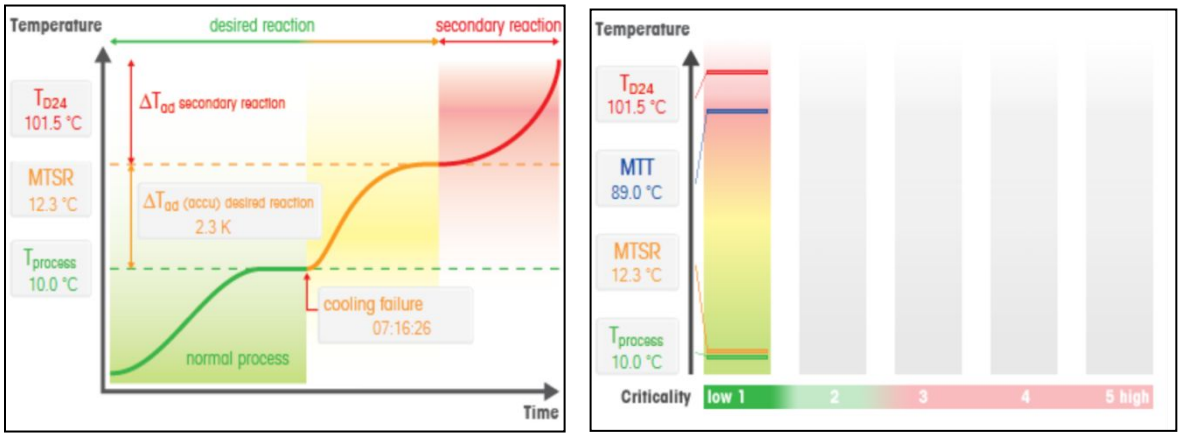


Fig 4. Trend of ammonia sparging (--- Tr; --- Tj; --- qr_rtc; ---Vr; ---Rt)

The data revealed, that the maximum heat rise during addition was 2.3 K with MTSR 12.3 °C and TD_{24} 101.5 °C which also reveals that the maximum temperature even after the cooling failure would reach to 53.0 °C (Fig 5a). The Stoessel's criticality class is 1 for the ammonia sparging operation, which states the reaction conditions are safe (Fig 5b). The temperature rise

during neutralization is a function of moles ammonia reacting which is controllable by a rate of sparging.



(a) (b)

Fig 5. (a) Runaway graph based on current values of ammonia sparging. (b) Stoessel's criticality class for ammonia Sparging.

2.3 Isolation of product and regeneration of reagent precursor:

The aforesaid operation follows filtration of ammonium *m*-chlorobenzoate salt leaving the *N*-oxide product in the filtrate. *N*-oxide was isolated by distillation of the solvent under reduced pressure (20 mm of Hg) at a temperature not exceeding 50 °C with 90% recovery of isopropyl acetate. The product purity was 98% by G.C in comparison with the standard. To ascertain the safety during distillation of solvent containing *N*-oxide, DSC of the isolated pure product as well as the product in iPrOAc at concentration 0.1 g/mL was studied. The onset point for pure and solvent phase was 326.42 °C and 330.18 °C which is a very high limit as compared to operating temperatures during distillation (Fig 6a and b).

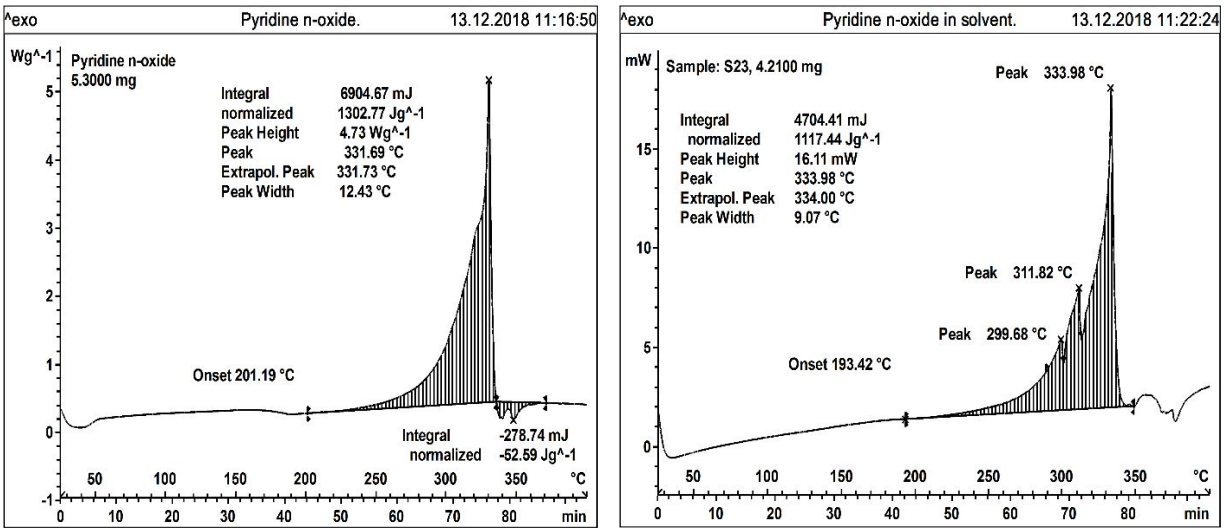


Fig 6. (a) DSC graph of pure pyridine *N*-Oxide; (b) DSC graph of pure pyridine *N*-Oxide in iPrOAc (0.1g/mL).

To recover *m*-chlorobenzoic acid from the salt, ammonium *m*-chlorobenzoate (452.4 g) was dissolved in 4.0 L of demineralized water followed by acidification with 580 mL 20 % HCl, filtration and drying at 95 °C till constant weight to yield *m*-chlorobenzoic acid 398.0 g, (96 % recovery, 99 % purity by HPLC). It is well known in the literature that *m*-chlorobenzoic acid can be recycled to *m*-CPBA.[28]

Kilo Scale protocol Development:

The RC1 trends revealed that the process can be scaled up in the equipment setup available for general purpose reactor. We scale up the reaction to 2.5 kg of pyridine input in 50 L glass reactor with suitable jacketed cooling arrangement and outlet connected to the common scrubber. Initial addition of pyridine to the isopropyl acetate showed no exothermicity using digital temperature indicator which substantiates observation in the RC1 experiment. The time taken for the addition of the first portion of *m*-CPBA (762.0 g) was 15 min with a temperature rise from 10 °C to 13

°C. After addition, the reaction mixture was aged for a further 10 min to stabilize to 10 °C. The same exothermic pattern was observed for subsequent 5 portions of *m*-CPBA. Further portions 7th to 10th showed a slight temperature rise of 1 °C. The operational procedure of aging the reaction mixture for 10 min after each addition of *m*-CPBA portion was followed even though the temperature was stabilized quickly. The addition of sodium sulfite also showed no exotherm, which indicates the complete consumption of *m*-CPBA. Even the equivalence ratio of *m*-CPBA used was 1.4 equiv., (75% w/w), which corresponds to 1.0 equiv. stoichiometrically. The crucial operation in the scale-up was ammonia sparging, where it can lead to rapid exotherm (Fig 4) but can be controlled by sparging rate. Based on RC1 data (Fig 4) were a rapid exotherm was observed at a sparging rate of 180-200 mL/min. Hence, for 2.5 kg input batch, initially sparging began with a low flow rate of 100-110 mL/min for 1 h. As no rapid exotherm was observed, the flow rate to 150-180 mL/min for a further 1 h and then to 180-200 mL/min where the similar exotherm pattern was observed. The filtration of the ammonium 3-chlorobenzoate salt was with no hurdles like caking or blocking filter pad. During solvent distillation, the thermic fluid bath temperature was maintained between 45-50 °C with a vacuum of 20 mm of Hg resulted in 90% solvent recovery and pyridine *N*-oxide (97% yield, 99.4% purity).

2.4 Scope of reaction

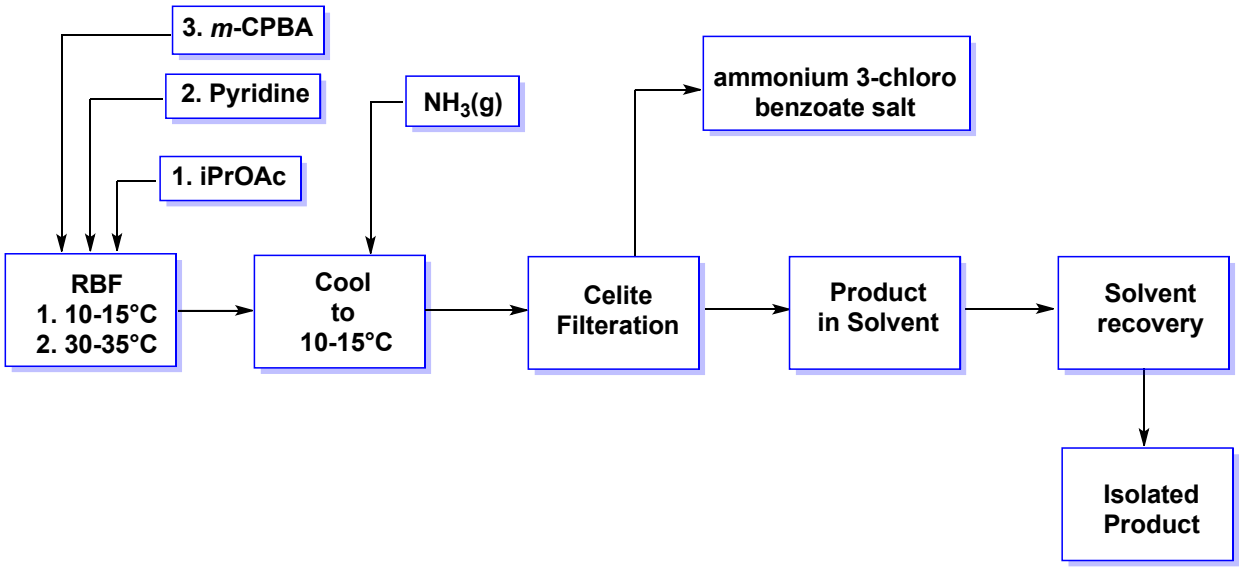
To investigate the scope and generality, the optimized protocol was extended to (substituted) pyridines and quinolines at the scale of 200.0 g (Table 4). The result reveals that the protocol is well suited for all the substrates which showed excellent yield and purity. The simplified schematic process flow is presented in Scheme 1. The DSC study for representative substituted pyridine *N*-oxide was also performed using a pure sample as well as a pure sample in iPrOAc, which ensures the process safety for the scope of reaction. Table 3 reveals the onset data of pure

product and heat release. For high energetic substrate 4-(4-nitrobenzyl) pyridine-*N*-oxide, 10b both DSC in pure form as well as DSC in iPrOAc was studied at higher concentration. In solution form, the endotherm was observed, since the product was insoluble at 0.5 g/mL concentration (refer to supplementary information). The onset for pure sample and in solvent form was 261.11 °C and 258.89 °C, respectively. which concludes that the isolation step during the solvent distillation is safe for this molecule.

Table 3: DSC data for substituted *N*-oxides

Entry	Substrate	Melting range (°C)	Onset Pure form (°C)	Heat Release (J/g)
1	1b	65-66	201.19	1302.77
2	3b	38-39	152.01	971.33
3	4b	183-185	202.16	1270.88
4	5b	162-163[a]	140.34	1087.53
5	9b	92-94	130.12	832.35
6	10b	153-155	173.38	457.34
7	12b	54-55	208.72	764.86
8	13b	68-69	125.64	856.86
9	14b	136-138	159.24	882.62

[a] Boiling point



Scheme 1. The process flow for *N*-oxidation of pyridine.

EXPERIMENTAL SECTION

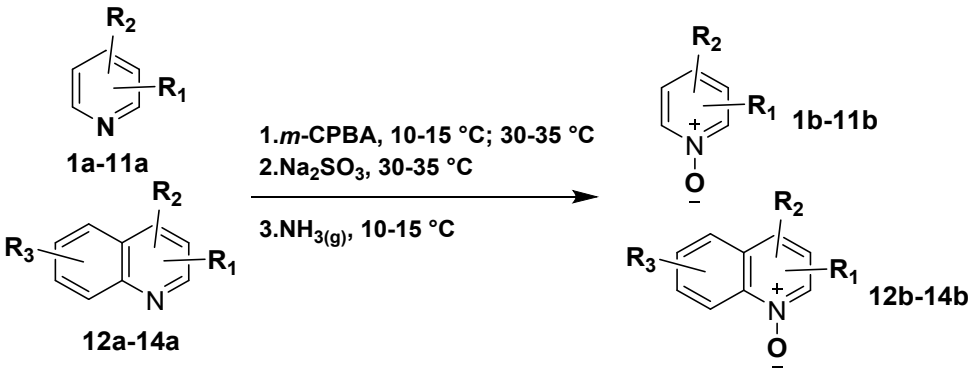
General Information

All reactions were carried out under the fuming hood. All the chemical and the reagents were obtained from Loba Chemie with a minimum purity of 99%, *m*-CPBA (75% w/w) and used as received. Melting point was recorded on Veego VMP-CM. Thin layer chromatography was done on pre-coated silica gel plates Kiesegel 60 F_{254} Macherey-Nagel). Gas chromatography was performed on Agilent 7890B with BP-5 column (30m X 0.32µm X 0.25 µm), injection temperature 240 °C, detector temperature 250 °C, initial temperature 100 °C for 2 min hold, final temperature 250 °C for 2 min hold, flow rate 1.2 mL/min, split ratio 83:1 and runtime 19 minutes. Peroxide content was checked on Macherey-Nagel Quantofix peroxide strips. The rate of flow of ammonia gas sparging was measured by Agilent ADM flow meter (G-6691-40500). FTIR spectra were recorded on Thermo Scientific Nicolet IS 5. NMR spectra were recorded on Agilent MR-400 using $CDCl_3$ or D_2O as a solvent and chemical shift reported as ppm downfield

to TMS. HRMS of the representative compounds were recorded using Thermofischer scientific Q-Exactive plus Biopharma-High resolution Orbitrap, by the direct infusion method. The isothermal study was carried on RC1e with the AP01-0.5-RTC-3w reactor, PTFE cover AP01-0.5, pitch blade stirrer 3-down. DSC measurements were performed with Mettler Toledo DSC 1 module, about 4mg of sample or solution 0.1 g/mL (unless stated) was taken in a 40µl high-pressure gold-plated crucible and measured with dynamic heating run from 25 °C to 400 °C. The nth order kinetic software is used to calculate activation energy and TMR.

Cautionary Note: Reactions and subsequent operations involving peracids should be performed behind safety shield on small scale. For relatively fast reactions, the rate of addition of oxidant should be controlled. The excess peroxide should be quenched with peroxide scavenger, before distillation.

Table 4. *N*-oxide formation of substituted pyridine and the *N*-heterocyclic substrate.



Entry	Substrate	Substitution			*N*-oxides	Yield (%)[c]	Purity(%)[b]	MP/BP[d] °C
		R_1	R_2	R_3				
1	1a	H	H	-	1b	98	99.6	65-66
2	2a	2-CH_3	H	-	2b	98.5	99.5	43-45

3	3a	3- CH_3	H	-	3b	98.4	99.4	38-39
4	4a	4-CH_3	H	-	4b	98.7	99.8	183-185
5	5a	2-CH_3	3- CH_3	-	5b	98.9	99.7	162-163[d]
6	6a	2-CH_3	6- CH_3	-	6b	98.2	99.9	108-110[d]
7	7a	3-CH_3	5- CH_3	-	7b	98.3	99.0	102-104
8	8a	2-$C_6H_5CH_2$	H	-	8b	98.4	99.4	95-97
9	9a	4-$C_6H_5CH_2$	H	-	9b	98.6	99.5	92-94
10	10a	4-$O_2NC_6H_4CH_2$	H	-	10b	98.5	99.8	153-155
11	11a	2-pyridyl	H	-	11b	98.6	99.8	295-298
12	12a	H	H	H	12b	98.6	99.5	54-55
13	13a	2-CH_3	H	H	13b	98.6	99.8	68-69
14	14a	H	H	8-OH	14b	98.2	99.8	136-138

[a]Experimental condition: substrate (200.0 g, 2.53 mol to 1.86 mol, 1.0 equiv.), 75% *m*-CPBA (610.0 g to 450.0 g, 3.53 mol to 2.60 mol, 1.4 equiv.), Na_2SO_3 (2g, 0.01 mol), isopropyl acetate (10 vol). [b]Purity by GC. [c]Isolated yield. [d]Boiling point.

General procedure for 200g scale.

In a 3L, 4 neck round bottomed flask arranged with an overhead stirrer and outlet connected with a trap containing 5% aq. oxalic acid, charged with pyridine (200.0 g, 2.52 mol) and isopropyl acetate (2.0 ltr, 10 vol.) under stirring at 125 RPM. The reaction mixture was cooled to 10-15 °C followed the addition of *m*-CPBA (75% w/w) (610 g, 3.53 mol, 1.40 equiv.) in 10 equal portions over a period of 45-50 minutes and stirred further for 1h at 10-15 °C. The reaction was further stirred at 30-35 °C for 4h. The reaction was monitored by GC. After completion of the reaction,

added solid sodium sulfite (2.0 g, 0.01 mol) to the reaction mixture and stir for 15 minutes. The peroxide content was determined by MN-Quantofix peroxide strip. The reaction mixture was cooled to 10-15 °C and anhydrous ammonia gas was sparged from the commercially available cylinder, at the rate of 180-200 mL/min till the pH was raised to 8-9 excess ammonia escaping was trapped in 5% aq. oxalic acid. The resultant slurry was filtered through Celite bed and washed with isopropyl acetate 2 x 200 mL. The filtrate was transferred to the rotary evaporator and the product was isolated by evaporation of solvent with 90% solvent recovery at 20 mm of Hg and temperature not exceeding 50 °C, which resulted in the viscous oily product which eventually crystallized on standing to furnish 235.0 g pyridine *N*-oxide (98% yield, 99.6% purity). The purity of the product was determined by G.C Melting point 65-66 °C; ^{1}H NMR ($CDCl_3$, 400MHz) δ 8.13 (dd, J = 5.4, 2.8 Hz, 2H), 7.21 (dd, J= 8.8, 6.4 Hz, 3H); FTIR (neat) 3361, 3108, 1733, 1716, 1653, 1605, 1558, 1540, 1506, 1460, 1223, 1171, 1070, 1015, 914, 832, 765, 672 cm^{-1}; HRMS elemental calculated for C_5H_5NO (MH^+):95.0371; found: 95.0371.

RC 1 reaction procedure:

The experiment was performed in an isothermal calorimetry in RC1e. Initially, isopropyl acetate (350.0 mL, 17.5Vol) was added followed by pyridine (20.0 g, 0.252 mol) under stirring at 300 RPM. The homogeneous solution was cooled to 10 °C and *m*-CPBA (61.0 g, 0.353 mol, 1.40 equiv.) was added in 10 equal portions and heat of reaction was recorded. Each portion of *m*-CPBA required approximately 2 mins for addition and we followed a trend of 5 min waiting after the addition of each portion. The reaction mixture was maintained at 10 °C for 90 min. The temperature of the reaction mixture was raised to 30 °C and was maintained for 1h. The excess peroxides were quenched by adding sodium sulfite (0.2 g, 0.001mol) and heat of peroxide quenching was recorded. The heat of peroxide quenching was negligible. The reaction mixture

was cooled to 10 °C and ammonia gas was sparged at the rate of 180-200 mL/min. During sparging at this rate, a rapid exotherm was recorded and the sparging was stopped to stabilize the reaction mixture temperature at 10 °C. The sparging of ammonia gas was continued at a low flow rate of 100-110 mL/min till the pH of the reaction mixture raised to pH 8-9 excess ammonia escaping was trapped in 5% aq. oxalic acid. The slurry was filtered through Celite bed and washed with isopropyl acetate 2 x 20 mL. The filtrate was transferred to the rotary evaporator and the product was isolated by evaporation of solvent which resulted in the viscous oily product which eventually crystallized on standing to furnish 23.3 g pyridine *N*-oxide (97% yield, 99.4% purity by GC). Melting point 65-66 °C

Kilo Scale Procedure:

In a 50L glass reactor with Teflon blade stirrer equipped in circulation bath with an external chiller of 14-16 L/min thermal fluid flow rate, was charged isopropyl acetate (43.7 L 17.5 Vol) followed by pyridine (2.5 kg, 31.64 mol) under stirring at 150 RPM. The reaction mixture was cooled to 10-15 °C. Maintaining the temperature 10-15 °C *m*-CPBA (75% w/w) (7.62 kg, 44.15 mol, 1.40 equiv.) was added in 10 equal portions. Each portion of *m*-CPBA was added in 15 mins and was aged for further 10 min before next addition. After complete additions, the reaction mass was maintained for further for 1h at 10-15 °C. The temperature of the reaction mixture was raised to 30-35 °C and was maintained for further 4h. The reaction was monitored by GC. After completion of the reaction, solid sodium sulfite (25.0 g, 0.19 mol) to the reaction mixture and stir for 15 minutes. The peroxide content was determined by MN-Quantofix peroxide strip. The peroxide test was negative. The reaction mixture was cooled to 10-15 °C and anhydrous ammonia gas was sparged from the commercially available cylinder, at the rate of 100-110 mL/min for 1h, then the rate was increased to 150-180 mL/min for further 1h and 180-200

mL/min for 2h maintaining the temperature of reaction mass at between 10-15 °C to achieve the pH of the reaction mass to pH 8-9. The excess ammonia was scrubbed using common scrubber facility. The resultant slurry was filtered through Celite bed on S.S 316L Nutsche filter and the cake was washed with isopropyl acetate 2 x 2.0 L. The filtrate was transferred to another 50L glass reactor and the solvent was distilled by maintaining the thermal fluid bath temperature at 40-45 °C under vacuum (20 mm of Hg). After complete distillation of solvent, the residue was degassed for 15 mins to ensure complete removal of solvent traces. The viscous oily product was unloaded hot in HDPE container which eventually crystallized on standing to furnish 2.92 kg pyridine *N*-oxide (97% yield, 99.4% purity). The G.C graph of kilo scale batch was concordant with the standard pyridine *N*-oxide. (refer supplementary information). Melting point 65-66 °C.

Conclusions

An improved, safe and scalable preparation and isolation process for *N*-oxides of (substituted)pyridines and quinolines with 98-99% yield with purity in the range of 98-99% using *m*-CPBA-$NH_{3(g)}$ system was developed. The safety of the reaction at conversion as well as isolation steps is substantiated by calorimetric data of reaction, isolated product. The proposed protocol is not only economic but also eco-friendly due to efficient recovery and reusability of the solvent as well as reagent precursor *m*-chlorobenzoic acid. The process flow is simplified with minimized utility, waste yielding high purity products are the key features of this protocol for scale-up which meets the industrial requirement of safety, cost-effectiveness. The improved heat capacity due to solvent: reactant ratio of 17.5, controlled addition of *m*-CPBA and ammonia, scavenging excess *m*-CPBA and cautious solvent recovery make the protocol to qualify most of the safety criteria. Hence, it was feasible for us to demonstrate the safe operation at scale as high as 2.5 kg batch.

ASSOCIATED CONTENT

Supporting Information

Supporting Information about spectral data and calorimetric analysis is available free of charge on the ACS Publications website

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