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A Novel, Safe, and Robust Nitration Process for the Synthesis of 4-(4-Methoxy-3-nitrophenyl)morpholine

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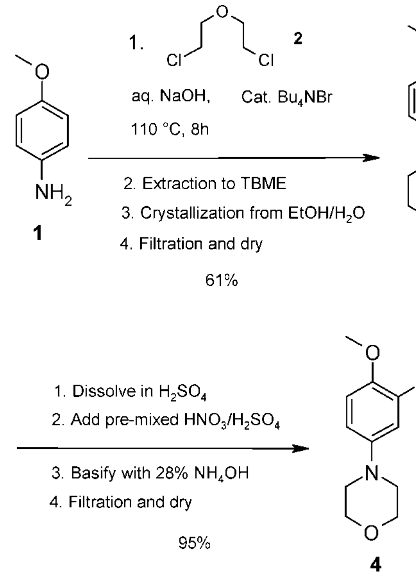
Abstract:

A novel nitration process was developed for the production of 4-(4-methoxy-3-nitrophenyl)morpholine. Crude 4-(4-methoxyphenyl-)morpholine produced in step 1 was converted to its nitric acid salt. The nitration reaction was carried out by adding a dichloromethane solution of the isolated salt to concentrated sulfuric acid. This protocol provided an easy and reliable way to obtain a 1:1 molar ratio of the substrate and nitric acid in the reaction mixture and was proven to be the most effective method to prevent under-/over-nitration. The incorporation of the protocol into the process resulted in substantial improvement of the robustness and safety profile of the whole process. In addition, 59% overall yield improvement, 30% capacity increase, 40% waste reduction, and simplified operations were achieved. A detailed thermal hazard analysis of the process was also performed.

Introduction

4-(4-Methoxy-3-nitrophenyl)morpholine (**4**) is a key intermediate for the synthesis of a drug candidate being developed to treat depression.[1] A two-step Kilo Laboratory process for **4** is summarized in Scheme 1.[2] Although the process was suitable to produce kilograms of **4** in early stage small scale campaigns, several issues were raised while planning for the development of a commercial scale process. For instance, the nitration was carried out by adding solid **3** to concentrated sulfuric acid. The dissolution of **3** into the acid is highly exothermic. This, coupled with a slow dissolution rate, makes the dosing of solid **3** a technical challenge on large scale. Poorly controlled addition would result in the accumulation of substrate and the formation of "hot spots" inside the batch, which in turn could lead to safety incidents and/or elevated impurity level. Furthermore, compound **3** is very active toward electrophilic substitution even in its protonated form. Over-nitration to 4-(4-methoxy-3,5-dinitrophenyl)morpholine occurred whenever nitric acid was overcharged. Under-/over-nitration not only caused yield loss but also created a big burden on the purification of the step product. Thus, strict chemostoichiometric control had to be enforced in the process, making the process far less robust. In order to achieve a 1:1 molar ratio of the substrate and nitric acid, every batch of **3** had to be analyzed for weight percent assay, nitric acid had to be titrated, and precise charge of the materials was required. However, even with extreme precautions under- or over-nitration (up to 6%) occurred several times during campaigns. Furthermore, to ensure a fast and clean nitration, a large excess of concentrated sulfuric acid (10 g/g of **3**) had to be used in the process. After the nitration a large quantity of base (28% NH$_4$OH) had to be used to neutralize the acid and to precipitate the product, resulting in lost capacity (maximum volume factor, 36 L/kg **4**) and the generation of huge amount of waste (total 83 kg of waste/kg **4**). Low yield (61%) and tedious isolation/purification procedures in step 1 were also opportunities for improvements. This article describes in detail how these issues were addressed during process development.

Scheme 1. **Kilo lab process**



Process Development

The optimization of step 1 was started with a thorough material balance analysis, which indicated that the major source of product loss was the mother liquor during the crystallization. Because the reaction was fairly clean, it was possible to eliminate the crystallization. Taking advantage of the fact that the product is a weak base, we used an old trick of acid extraction/basification procedure as an easy way to isolate the solid product and to remove any nonbasic impurities in the crude product. Thus, upon the completion of the reaction the mixture was cooled to ambient temperature, diluted with water, and extracted with TBME and ethyl acetate. The combined organic solution was washed with water and then was extracted with

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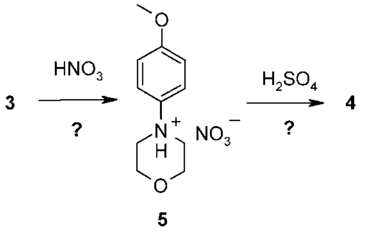
Table 1. **Different conditions of converting 5 to 4**[a]

entry	solvent	concn of **5** solution (g/mL)	**5**:H_2SO_4 (g/g)	temp (°C)	additives	area %[d] **4**	area %[d] **6**	area %[d] total others	isolated yield (%)
1	AcOH	0.5	1:4	0 ± 5		70	3	27	
2	AcOH	0.35	1:4	0 ± 5		59	7	34	
3	AcOH	0.4	1:4	0 ± 5	Ac_2O	61	18	21	
4[c]	AcOH	0.4	1:4	0 ± 5	Ac_2O	0	66	33	
5	AcOH	0.4	N/A	20	AcCl	0	94	6	91
6	AcOH	0.4	N/A	0 ± 5	AcCl	2	80	18	
7	CH_3NO_2	0.25	1:3.5	0 ± 5		94	0	6	91
8	CH_3NO_2	0.2	1:4	0 ± 5		89	0	11	93
9[c]	CH_3NO_2	0.2	1:4	0 ± 5		9	31	60	
10	CH_2Cl_2	0.2	1:4	0 ± 5		97	0	3	
11	CH_2Cl_2	0.2	1:4	0 ± 5		98	1	1	95
12	CH_2Cl_2	0.16	1:4	0 ± 5		95	0	5	94
13	CH_2Cl_2	0.16	1:2	0 ± 5		69	7	24	

[a] Unless otherwise indicated, the reaction was carried out by adding a solution of **5** in the specified solvent to concentrated sulfuric acid. [b] Isolation of product was not attempted. [c] The reaction was carried out by adding sulfuric acid to a solution of **5**. [d] HPLC area percent measured at wavelength of 272 nm.

Scheme 2. **Proposed nitration protocol**



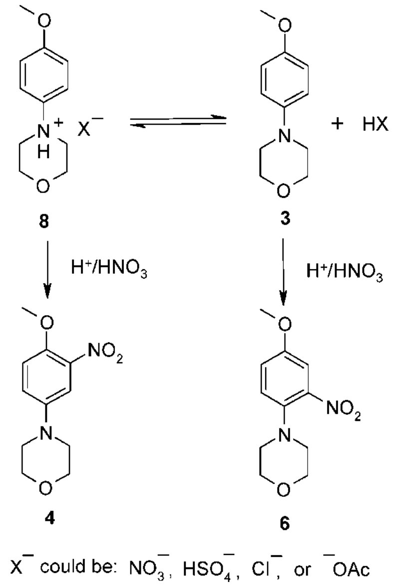
10% HCl. The aqueous solution was added to 10% NaOH solution to precipitate the product. After filtration, washing, and drying, product **3** was obtained in 91% yield with excellent purity.

The key to prevent under-/over-nitration was to have a 1:1 molar ratio of **3** to nitric acid in the reaction mixture. Noticing that **3** is a mono-base, we envisaged that if we could prepare the nitric acid salt of **3** (structure **5** in Scheme 2) and then convert the salt to **4** we might be able to address most of the current process issues. First, the isolated salt should be a mixture of nitric acid and the substrate with exact 1:1 ratio, and therefore, under-/over-nitration could be prevented. Second, the sulfuric acid charge could be significantly reduced if the dried salt (**5**) were used. In the Kilo Laboratory process 70% HNO_3 was used. At the end of the reaction, 60% of water in the reaction mixture came from the water in nitric acid and 40% was generated in the reaction. Therefore, the reaction system would contain 60% less water if the dried **5** were used. Accordingly, we might be able to reduce sulfuric acid charge by 60% and still achieve the same results. To make the salt, 1.0 equiv of 70% HNO_3 was slowly added to a solution of 10 g of **3** in 50 mL of TBME and 15 mL of THF at around 0 °C. A solid precipitated out during the addition. After the addition the solid was isolated and dried to give **5** in quantitative yield.

The conversion of **5** to **4** was studied under different conditions. Some of the examples are summarized in Table 1. For most of the experiments in the table a solution of **5** in a solvent was prepared, and then this solution was added to concentrated sulfuric acid. The substrate to sulfuric acid ratio was 1:4 (g/g) in most of the experiments. Exceptions are entries 5 and 6, in which acetyl chloride was added to a solution of **5** in acetic acid, and entries 4 and 9, in which sulfuric acid was added to a solution of **5** in either acetic acid or nitromethane. The HPLC area percent of the desired product **4**, its regioisomer **6**, and the sum of all other peaks (as impurities) in the reaction mixture are listed in the table. *In all of the examples no dinitrated product was detected.* As indicated in the table, acetic acid was not a good solvent for the reaction. Addition of an acetic acid solution of **5** (at a concentration of 0.5 g/mL) to sulfuric acid at around 0 °C led to the formation of a mixture containing 70 area % of **4** and 3 area % of **6**, together with 27 area % of unidentified impurities (entry 1). The formation of more **6** and impurities was observed when a more dilute solution (0.35 g/mL) was used (entry 2). When a 0.4 g/mL solution of **5** in acetic acid was added to a mixture of sulfuric acid and acetic anhydride (used as water scavenger), a higher percentage of **6** was formed (entry 3). When sulfuric acid was added to a solution of **5** in acetic acid, no product **4** was observed in the reaction mixture and **6** was formed along with significant amount of impurities (entry 4). The nitration reaction could also be effected by adding acetyl chloride to acetic acid solution of **5**. However, under these conditions compound **6** was the major product (entries 5 and 6). In entry 5, compound **6** was isolated in 91% yield. Nitromethane is a good solvent for the reaction. When a solution of **5** in nitromethane was added to sulfuric acid at around 0 °C, the reaction was much cleaner and produced only the desired isomer **4**. Product **4** was isolated in excellent yield (91–93%, entries 7 and 8). Again, addition of sulfuric acid to the solution of **5** in nitromethane was not a good option, as indicated in entry 9. The best results were obtained by adding a solution of **5** in dichloromethane to sulfuric acid at around 0 °C (entries 10–12). In these cases, the reaction mixture was very clean and **4** was isolated in ~95% yield. Thus, dichloromethane was chosen for the process. It seemed very important to keep substrate to sulfuric acid ratio at 1:4 (g/g). Lowering the sulfuric acid charge might increase the formation of **6** and other impurities, as illustrated in entry 13.

The regioselectivity of the reaction was interesting. As indicated in the table, a higher level of **6** was generated when acetic acid was used as solvent. In all of the batches in which a solution of **5** was added to concentrated sulfuric acid, the reaction produced **4** as major product. In the batches without sulfuric acid or the batches in which sulfuric acid was added

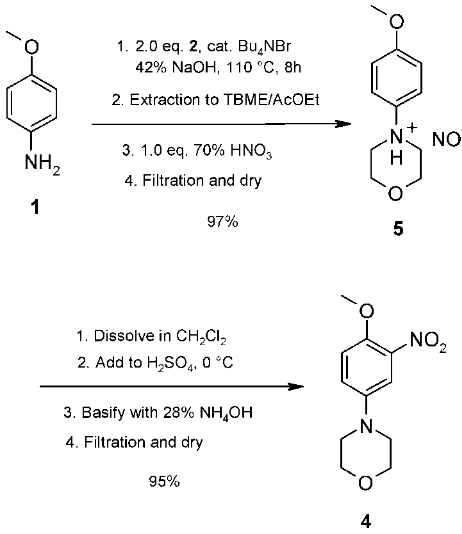
Scheme 3. **Formation of regioisomers**



to a solution of **5**, compound **6** was the major product. This might be explained using Scheme 3. There is an equilibrium between **3** and its salt **8**. For the nitration of **3**, the amino group controls the selectivity and facilitates the formation of compound **6**. For the nitration of **8**, the methoxy group dictates the regioselectivity, and therefore **4** will be produced. Compound **3** is much more reactive than **8**. Any significant presence of **3** in the reaction mixture will result in its nitration to afford **6**. The consumption of **3** will then shift the equilibrium to the right. As a result, **6** may be formed as a major or even the sole product. In the cases where a solution of **5** was added to sulfuric acid, the concentration of **3** should be extremely low and **4** should be the major product. When sulfuric acid is added to a solution of **5**, the initial concentration of the acid is strong enough to initiate the nitration reaction but not strong enough to substantially reduce the concentration of **3** in the reaction mixture, so that the formation of **6** is significant.

We found that a good quality **5** could be prepared by adding 70% nitric acid directly to the TBME/ethyl acetate extract of the crude **3** from step 1 (Scheme 1). This added more advantages to the process by eliminating the isolation of free base **3**. Our final version of the new process is illustrated in Scheme 4. Upon the completion of the free base (**3**) formation, the reaction mixture was cooled and extracted with TBME and ethyl acetate. The combined organic solution was cooled to around 0 °C, and to it was slowly added 1.0 equiv (relative to **1**) of 70% HNO_3 to generate **5**, which precipitated out from the solution immediately upon the acid addition. Compound **5** was filtered and dried at ambient temperature under vacuum. Compound **5** was then dissolved in CH_2Cl_2, and the solution was slowly added to concentrated sulfuric acid (4 g/g of **5**) while maintaining the batch temperature at 0 ± 5 °C. After the addition the mixture was stirred for approximately 30 min, and then the acid layer was slowly transferred to cool water. To the diluted acid solution at <10 °C was added 28% NH_4OH solution until pH >10. The precipitated product was filtered, washed with water, and dried under vacuum to give **4** in excellent yield and purity.

Scheme 4. **New process**



Safety Evaluation

A detailed thermal hazard analysis was conducted for the process. All reaction enthalpy measurements were carried out using a Mettler RC1 reaction calorimeter, and all thermal stability data were generated using an ARC2000 adiabatic calorimeter (slope sensitivity = 0.2 °C, hastelloy bomb).

Addition of 3 to Concentrated Sulfuric Acid. As a reference, the addition of solid **3** to concentrated sulfuric acid, an operation employed in the Kilo Laboratory process, was studied. The addition was exothermic and reaction enthalpy was determined to be 120 kJ/g-mol **3**. On the basis of an experimental determination of specific heat capacity at constant pressure (c_p), the adiabatic temperature rise was estimated at 70 °C. Thermal stability studies indicated a self-heating exotherm onset at 150 °C with a calculated adiabatic temperature rise of >70 °C. A sharp pressure rise was observed at around 150 °C, indicating exothermic decomposition. Because the process was typically run at <20 °C, an accidental total charge of **3** could raise the batch temperature to 90 °C, still leaving a greater than 50 °C safety margin from the onset temperature. However, as mentioned earlier, the dissolution of **3** in concentrated sulfuric acid was very slow. This may easily lead to the accumulation of the substrate and create locally overheated "spots" that could cause significant material decomposition inside the batch if the addition of the solid could not be properly controlled.

Reaction Calorimetry of Addition of 70% HNO_3 to a Solution of Free Base 3 in TBME/Ethyl Acetate. The addition was determined to be exothermic, and reaction enthalpy was measured to be 55.3 kJ/mole of **5**. On the basis of an experimental determination of c_p, the adiabatic temperature rise was estimated to be 33.8 °C. The reaction mixture became a thick slurry as the addition progressed, but energy release was addition-controlled. The addition was performed at 0–5 °C, and the maximum theoretical temperature of the batch assuming loss of cooling is 33.8 °C. Because the dried **5** has a self-heating exothermic onset at 119–130 °C, a safety margin of >60 °C exists in a worst case scenario (the full adiabatic temperature rise is reached). The process can therefore be run safely.

Stability of Salt 5. The thermal stability of dried solid **5** was measured in ARC experiments, which indicated an onset temperature of 120–130 °C over two different experiments with different thermal inertia factors. The exotherm is energetic with fast release of energy and decomposition as demonstrated by a sharp rise in pressure under complete containment. However, in the new process the salt was generated at around 0 °C and was dried at approximately 20 °C, permitting the standard >50 °C safety margin. Additionally, dried **5** was tested for sensitivity to impact using a dropping weight protocol. The material was found to be insensitive to impact at the maximum test height of the apparatus over 10 repeated runs, indicating that the material is safe for normal handling.

Reaction Calorimetry and Thermal Stability of Addition of Dichloromethane Solution of 5 to Concentrated Sulfuric Acid. The addition and reaction were determined to be exothermic, and reaction enthalpy was determined to be 243.5 kJ/mole of **5**. On the basis of an experimental determination of c_p, the adiabatic temperature rise was estimated to be 61.3 °C. The reaction mixture consisted of two liquid phases, and under sufficient agitation the rate of heat evolution was found to be addition controlled over ~30 min of addition time. No significant residual (post-addition completion) reaction enthalpy was observed. Post reaction completion the reaction mixture was tested for thermal stability. The data indicated an exotherm onset of 98.7 °C and a time to maximum rate from initiation of approximately 200 min. Additionally there was a rapid pressure buildup (under complete containment), indicating exothermic decomposition. The normal process temperature was 0 °C. Therefore, if all of the dichloromethane solution of **5** was to be charged instantly, the batch temperature could spike to 61.3 °C, which is less than the standard 50 °C margin from the onset temperature. However, because of the absence of delayed reaction exotherms and the fact that the rate of heat evolution is substantially addition-controlled, the process can be run safely.

Drying of 4. Thermal stability of **4** was tested. A self heat exotherm was detected with an onset temperature of 165 °C and a predicted adiabatic temperature rise of >430 °C was observed. The highest exposed temperature in the process for **4** was 45 °C (drying temperature). Therefore, there is a sufficient safety margin for safe drying of the step product.

Conclusion

To the best of our knowledge, this is the first example of carrying out nitration using isolated nitric acid salt of a substrate. This approach provides an ease and reliable way to obtain an exact 1:1 molar ratio of substrate and nitric acid, which may be otherwise difficult to achieve especially on a manufacturing scale using fixed equipment. In our case, this method has been proven to be the most effective way to prevent under-/over-nitration and thus contributed to the substantially improved robustness of the process. Furthermore, the incorporation of the method added other benefits to the whole process. For instance, direct precipitation of **5** from the step 1 extract resulted in the elimination of solvent exchange and crystallization operations used for the isolation of free base **3** in step 1. The replacement of charging solid **3** to sulfuric acid with addition of a dichloromethane solution of **5** to sulfuric acid made the process safer and more operation friendly. The operations of premixing of nitric acid with sulfuric acid and charging of the mixed acid to the batch were eliminated from the process. The sulfuric acid charge was reduced by 60%, which in turn led to 30% reduction of maximum operation volume (25 vs 36 L/kg **4**) and 40% reduction of total generated wastes (50 vs 83 kg/kg **4**). More importantly, ~59% yield improvement over the two steps (from 58% to 92%) was achieved. Thermal hazard analysis of the key intermediates and key operations has concluded that the process is safe to run under the operation conditions. An ongoing study has shown that this nitration protocol can be applied to a variety of substrates, and the results will be reported in a separate paper.

Experimental Section

4-(4-Methoxyhenyl)morpholine, Nitric Acid Salt (5). A 1-L, 4-neck round bottom flask, equipped with a mechanical stirrer and a nitrogen inlet, was charged with 20 g (0.162 mol) of *p*-anisidine, 48 g (0.336 mol) of 2-chloroethyl ether, 1.04 g (0.003 mol) of tetrabutylammonium bromide, and 77 g (0.8 mol) of 42% sodium hydroxide solution. The mixture was refluxed at around 110 °C for about 8 h. After completion of the reaction was confirmed, the mixture was cooled to 20 °C and extracted with 50 mL of TBME and 50 mL of ethyl acetate, respectively. The combined organic solution was washed with 80 mL of water. The organic solution was cooled to 0 ± 5 °C, and to it was slowly added 14.6 g (0.162 mol) 70% HNO_3. A heavy precipitation was formed at the late stage of the addition. After the addition the batch was aged for at least 1h. The solid was filtered, washed with 40 mL of TBME, and dried under vacuum at 45 °C overnight to give 40.2 g (97%) **5** as a tan solid.

4-(4-Methoxy-3-nitrophenyl)morpholine (4). A 250-mL, 4-neck round bottom flask, equipped with a mechanical stirrer and a nitrogen inlet, was charged with 80 g (0.815 mol) of 95% sulfuric acid. The acid was cooled to ~0 °C. A solution of 20 g (0.078 mol) of **5** in 125 mL of dichloromethane was slowly added to the acid while the batch temperature was maintained at 0 ± 5 °C. After the addition the mixture was stirred for 30 min. The agitation was stopped, and the bottom acid layer was separated. The acid solution was slowly added to 200 mL of water while maintaining the temperature at <10 °C. To this diluted acid solution was then slowly added 190 mL of 28% NH_4OH solution while the temperature was maintained at <10 °C. At the end of the addition the pH of the mixture should be higher than 10. The batch was aged at 5 ± 5 °C for 1 h. The solid was filtered, washed with 50 mL of water, and dried under vacuum at 45 °C overnight to give 17.5 g (94% yield) of **4** as an orange solid.

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Supporting Information Available

Process hazard analysis data. This information is available free of charge via the Internet at http://pubs.acs.org.

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