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Scale-Up of the Nitration of 1-Acetyl-3,4-dichloro-1,2-(ethylenedioxy)benzene Using Nitric Acid/Trifluoroacetic Acid

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Abstract:

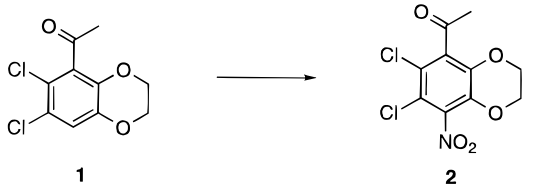
The process development of the nitration of 3-acetyl-4,5-dichloro-1,2-(ethylenedioxy)benzene (1) to 3-acetyl-4,5-dichloro-1,2-(ethylenedioxy)-6-nitrobenzene (2) led to two potential scale-up processes. The two nitration processes were a solids addition to nitric acid and nitric acid addition to a trifluoroacetic acid solution. The detailed hazards safety evaluation of the two processes was carried out using abuse studies, CHETAH calculations, the reactive system screening tool, accelerating rate calorimetry, and differential scanning calorimetry. The nitric acid addition to a trifluoroacetic acid solution process was chosen because of the better safety profile. This process was successfully scaled up in a pharmaceutical pilot plant.

Introduction

The nitration of an aromatic nucleus is a commonly used reaction in organic synthesis. Many methods have been developed to carry out nitrations.[1] The application of various nitration methods for small scale can be conducted without serious concern for safety issues, but as the scale is increased, the concern for safety issues becomes increasingly important.[2] In a pharmaceutical pilot plant, safety concerns are certainly a major issue that has to be carefully addressed before a chemical process is conducted. Nitrations immediately raise greater safety concerns compared to the average process conducted in pharmaceutical pilot plants. Besides the normal safety concerns, the very serious safety concerns stem from a long history of safety problems associated with nitration reactions which have led to runaway reactions, explosions, or product stability problems.[3]

Most pharmaceutical pilot plants do not include bunkered reactors to provide safety for personnel and the facility; therefore, nitrations are typically discouraged. Contracting out nitrations to a manufacturer specializing in nitrations is an attractive alternative to doing the chemistry in-house on pilot plant scale. However, commercial pressures on pharmaceutical companies have forced the shortening of time lines to develop clinical compounds, which has increased the pressure to supply compound both more quickly and in larger quantities sooner. It is, therefore, desirable to be able to run nitrations safely in a pharmaceutical pilot plant to meet this need for fast development which cannot always be met by using a contractor. Rapid process development and safety evaluation are keys to achieving this goal.

The synthesis of a pharmaceutical clinical candidate required the nitration of 3-acetyl-4,5-dichloro-1,2-(ethylenedioxy)benzene (**1**) to 3-acetyl-4,5-dichloro-1,2-(ethylenedioxy)-6-nitrobenzene (**2**).[4] The development program required kilograms of drug substance, and thus a safe process suitable for the pilot plant production of multiple kilograms of intermediate **2** was needed. We report the development of a safe nitration procedure in this paper.



Process Development

The development of a process for the conversion of **1** into **2** began with exploratory chemistry defining the conditions needed for this nitration. In Table 1, a variety of experiments are reported which exemplify some of the conditions tried. Acetic acid (entry 1) was tried as the solvent but gave poor-quality product. Acetic acid was anticipated to be a poor solvent choice on the basis of safety considerations, because there have been reported safety problems with nitric acid/acetic acid mixtures.[5] Sulfolane (entries 2−4) was used as the solvent, but at 0−5 °C the nitration did not take place, and at higher temperatures the reaction gave some product, but it was quite impure. Methylene chloride (entries 5 and 6) was used as the solvent with the idea that the separate organic phase would help protect the product from the harsh conditions in the inorganic phase. Concentrated 70% HNO_3 did not react with **1**, but fuming 90% HNO_3 worked quite well, producing a 78% yield of **2**. Upon further investigation it was found that, unfor-

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(1) Reviews: (a) Askani, R.; Taber, D. F. *Compr. Org. Synth.* **1991**, *6*, 103. (b) Sauve, G.; Rao, V. S. *Compr. Org. Funct. Group Transform.* **1995**, *2*, 790. (c) Ridd, J. H. *Acc. Chem. Res.* **1971**, *4*, 248. (d) Suzuki, H. *Synthesis* **1977**, 217. (e) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration Methods and Mechanisms*; VCH Publishers, Inc.: New York, 1989. (f) Hoggett, J. G.; Moodie, R. B.; Penton, J. R.; Schofield, K. *Nitration and Aromatic Reactivity*; Cambridge University Press: Cambridge, 1971. (g) Bretherick, L. *J. Chem. Educ.* **1989**, *66* (9), A220.

(2) (a) Zeller, J. R. *ACS Symp. Ser.* **1985**, *274*, 107. (b) Hoffmann, W. *Chimia* **1989**, *43*, 62. (c) Brummel R. N. *Plant/Oper. Prog.* **1989**, *8* (4), 228.

(3) (a) Bretherick, L. *Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth-Heinemann Ltd: Oxford, 1995; Vol. 1, p 1463; (b) Vol. 2, p 231. (c) Kuilin, A.; den Hartog, J. A. J. *Chem. Eng. News* **1989**, *67* (5), 2. (d) Andreozzi, R.; Aquila, T.; Caprio, V.; Insola, A. *Thermochim. Acta* **1992**, *199*, 159.

(4) Clark, R. D.; Jahangir, A.; Flippin, L. A.; Langston, J. A.; Leung, E.; Bonhaus, D. W.; Wong, E. H. F.; Johnson, L. G.; Eglen, R. M. *Bioorg. Med. Chem. Lett.* **1995**, *5* (18), 2119.

(5) (a) Raikova, V. M. *Chem. Abstr.* **1983**, *98*, 5958. (b) Reference 3a.

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Table 1. **Various solvents used for the nitration of 1**

entry	solvent	HNO_3 (mL/g)	time (h)	temp (°C)	result
1	HOAc	1	0.33	0−5	oiled out product
2	sulfolane	1	0.5	0−5	no reactn
3	sulfolane	1	1.5	30−35	some product
4	sulfolane	1	0.33	60−70	mixture of products
5	CH_2Cl_2	0.7[a]	1, 2	0−5, rt	no reactn
6	CH_2Cl_2	1	1	0−5	78% purified **2**
7	H_2SO_4	0	0.75	rt	**1** stable to H_2SO_4
8	H_2SO_4	0	1	rt	**2** stable to H_2SO_4
9	H_2SO_4	0.3	0.33	0−5	black reactn mixture, multiple products

[a] 70% HNO_3.

Table 2. **Addition of 1 to nitric acid**

entry	g of **1**/mL of HNO_3	time (min)	temp (°C)	yield of **2** (%)	comments
1	0.25[a]	60	0−5	60	not pure
2	0.25[a]	30	rt	64	good
3	0.25[a]	180	rt	61	good
4	0.25	15	23−40	76	minor impurity
5	0.25	15	0−10	91	trace impurity
6	1	15	0−10	94	good
7	1	10	−20 to −14	94	pure
8	0.5	70	−18 to −14	95	pure
9	0.33	70	−20 to −13	94	pure
10	1	10	22−50	85	good
11	1	5	70−75	no crystals	brown gas
12	1	18 h, 15	rt, 105	0	complete dec of **2**

[a]70% HNO_3.

Table 3. **Nitration of 1 in TFA**

entry	equiv of HNO_3	time (h)	temp (°C)	yield of **2** (%)	comments
1	1.5	18	2−5	92	good
2	1.3	1, 2	2−5, rt	88	good
3	1.3	1, 17	2−5, rt	88	good
4	1.5	1, 17	2−5, 50	85	some impurities
5	1.3	3	55−72	85	some brown gas, 72% pure
6	2.2	6	55−60	0	no **2**

tunately, methylene chloride has been reported to form explosive mixtures with nitric acid, and thus, it was not investigated further.[6] Traditionally, sulfuric acid/nitric acid mixtures have been used for nitrations. The stability of **1** and **2** in sulfuric acid (entries 7 and 8) was tested and determined not to be a problem. However, sulfuric acid/nitric acid mixtures gave very poor nitration results (entry 9).

A promising nitration process based on adding **1** as a solid to nitric acid with no other solvent present was developed (see Table 2). With 70% HNO_3 (entry 1) at 0−5 °C the process gave encouraging results. The process at rt (entries 2 and 3) produced good-quality **2** but in modest yield. Significant improvement came by switching to 90% nitric acid. Using 90% HNO_3, the process was optimized (entries 4−9). At 23−40 °C (entry 4) the nitration worked with better recovery than the 70% HNO_3 experiments but gave somewhat impure product. Lowering the temperature (entry 5) gave substantially improved yield and product purity. Increasing the concentration of **1** (entry 6) gave very good yields and high-quality product. The temperature was further lowered (entry 7), which gave excellent yield and purity. In this experiment, the consumption of starting material **1** was checked 30 s after 80% and 100% addition of **1**. At 80% and 100% there was only a trace of **1**, proving that the reaction was very fast and no significant quantity of **1** was building up. Therefore, the heat of the nitration could be easily controlled by the addition rate of **1**, which was viewed as an important safety parameter. One potential scale-up problem foreseen was that the solution became thick when about $^2/_3$ of **1** had been added and nitro product **2** started crystallizing out of solution. The dilution was increased (entries 8 and 9), which did thin the reaction solution but did not prevent **2** from crystallizing out, still making the solution somewhat thick. Another problem on scale-up was anticipated to be the difficulty of adding a solid powder to a pilot plant reactor while the nitration is underway. While this can be accomplished, the clogging of addition apparatus and difficulty of not exposing operators could be troublesome. Several small-scale abuse studies (entries 10−12) were carried out in an effort to determine runaway potential and high temperature reaction solution stability. It was clear that high temperatures resulted in decomposition of the product but runaway reactions did not occur on the scale investigated. Moderate scale-up (100−1000 g) of process using the conditions in entries 7−9 proved the viability of this process and did not reveal any unforeseen problems. The scale-up runs also served to satisfy a second purpose in supplying immediate demands for material.

Trifluoroacetic acid (TFA) has been seldom used as a solvent for nitrations even though it is a good solvent and is resistant to oxidation.[7] It was found to be an excellent solvent in which to run the nitration (see Table 3). The process did not require a large excess of nitric acid to achieve an excellent yield of **2** (entry 1). The excess HNO_3 was further minimized (entry 2) but required increasing the temperature to drive the consumption of **1** to completion. The reaction time was increased (entry 3), which slightly altered the quality of **2** by reducing the level of residual **1**, but not significantly changing the overall quality. Several high-temperature abuse experiments (entries 4−6) were carried out and did not indicate any serious problems. Product **2** was still obtained from these reactions where the nitric acid was limited to 1.5 equiv. Product **2** was consumed by excess nitric acid if present (entry 6); therefore, limiting the supply of nitric acid was considered a valuable precaution. The process used in entry 2 was scaled up (100−1000 g) without any significant problems or yield loss.

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(6) (a) Andrussow, L. *Chim. Ind. (Paris)* **1961**, *86*, 542. (b) Bretherick, L. *Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth-Heinemann Ltd: Oxford, 1995; Vol. 1, p 1475.

(7) (a) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration Methods and Mechanisms*; VCH Publishers, Inc.: New York, 1989; p 21. (b) Schofield, K. *Aromatic Nitration*; Cambridge University Press: Cambridge, 1980; p 37.

Table 4. **CHETAH results**

entry	sample	max heat of dec	fuel value	O_2 balance	CHETAH ERE criterion 4	overall energy release potential	net plosive density
1	**2**	high	high	high	medium	high	plosive
2	mixture A	high	high	high	medium	high	plosive
3	mixture B	medium	medium	high	medium	high	unknown

Safety Evaluation

The two processes that were considered for nitration of **1** for pilot plant operation were the solids addition to 90% nitric acid (Table 2, entry 7, defined as mixture A) and the use of TFA as the solvent (Table 3, entry 2, defined as mixture B). Both processes efficiently convert **1** into **2** and would be amenable to pilot plant operations. The decision between the two alternatives had to be made on the basis of a careful evaluation of the safety of each process. The first step in evaluation of these two processes was evaluating the data already generated in the abuse studies. The abuse studies for both processes indicated severe product decomposition at high temperatures and gas evolution but did not indicate any severe uncontrollable problems. No clear distinction between the safety of the two processes could be concluded from these abuse studies.

The next step in a safety profile for these reactions was using an inexpensive and convenient computer program called CHETAH.[8] This program provided a calculated chemical thermodynamic and energy release evaluation (ERE). In Table 4, the results from CHETAH calculations are summarized. The nitro intermediate **2** (entry 1) was classified as plosive and had high ratings in four of the other five categories. This suggested caution and that further testing should be undertaken to determine its sensitivity. This result was expected as the calculations/ratings are conservative. Mixture A (entry 2) had the same ratings profile as nitro intermediate **2**. Mixture B (entry 3) did not exceed the threshold in the net plosive density to rate plosive and was medium in three of the five other categories. The high rating in the oxygen balance also may be unjustified as small molecular weight carboxylic acids are unjustly rated in this category.[8] The conclusions from this calculation-driven evaluation were that the nitro intermediate **2** needed close scrutiny and that the nitration in TFA (mixture B) seemed inherently less dangerous than the nitration in the solids addition mixture (mixture A).

Our process hazards evaluation also used methods designed to specifically evaluate safety parameters. The reactive system screening tool (RSST) was used to evaluate the exothermic behavior of reaction mixtures as they were slowly warmed up, monitoring the pressure and temperature. In Table 5 are the three key experiments using this technique. All of the mixtures, except entry 2, were heterogeneous, making stirring difficult. The corrosive nature of the hot nitric acid was particularly destructive to the equipment, occasionally leading to equipment failure. Final reaction mixtures were screened for any subsequent chemistry occurring at higher temperatures that might pose a safety hazard from generation of rapid heat or pressure. For entry 1, the nitration mixture produced one exotherm with an onset at 45−50 °C, producing a pressure and temperature rise with a maximum dP/dt of 23 psi/min at 105 °C and maximum dT/dt of 43 °C/min at 108 °C. The reaction also produced noncondensable gas. This exotherm was a concern but did not rule out this procedure because of the fair margin of safety between the reaction temperature (−14 °C) and the onset of the exotherm. In entry 2, the compatibility of trifluoroacetic acid and nitric acid was tested, and this combination did not produce any measurable pressure or temperature rise. In entry 3, mixture B was tested, and the results were very encouraging because only small dT/dt and dP/dt were found. Noncondensable gas was formed but only slowly. These results did not eliminate either procedure but demonstrated the reduced exothermic behavior of the TFA/HNO_3 reaction system.

Table 5. **RSST results**

entry	sample	exotherm onset (°C)	noncondensable gas formed
1	mixture A	45−50	yes
2	TFA/HNO_3	none	no
3	mixture B	55−60	yes

Table 6. **ARC results**

		temp (°C)		
entry	sample	$dT/dt = 0.05$ °C/min[a]	$dT/dt = 0.1$ °C/min	$dT/dt = 0.2$ °C/min
1	**2**	215−218	233	242
2	mixture A	<37	49	62
3	TFA/HNO_3	158−161	180	
4	mixture B	35−37	44	

[a] Exotherm onset.

A more detailed inspection of the chemistry that occurs at temperatures higher than the reaction conditions was carried out using accelerating rate calorimetry (ARC). See Table 6 for results from four key ARC experiments. The stability of the nitro product **2** (entry 1) was good, and significant decomposition heat rates did not occur until the temperature exceeded 200 °C. Evaluation of reaction mixture A (entry 2) revealed that, even at the start temperature of 37 °C, the mixture was self-heating (0.08 °C/min). The time to reach 200 °C under adiabatic conditions was calculated to be only 36 min. The pressure data was also alarming; at 160 °C, $dP/dt = 100$ psi/min, and at 185 °C, $dP/dt = 1000$ psi/min. These results indicated a hazardous exotherm if reaction control was ever lost. In entry 3, the mixture of TFA/HNO_3 did not rapidly decompose below 150 °C and was only slightly exothermic starting at 158−161 °C. For reaction mixture B (entry 4), there was onset of

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(8) CHETAH, version 7.0, 3rd ed., by American Society for Testing and Materials, 1994.

exothermic activity at 35−37 °C, but the maximum self-heat rate was only 0.18 °C/min. The adiabatic temperature rise for this exotherm was calculated to be 48 °C, making the final temperature only 78 °C. This mild exotherm displayed did not constitute a serious safety concern. The ARC results clearly favor the TFA/HNO_3 reaction mixture on the basis of safety concerns if reaction control were ever lost.

Differential scanning calorimetry (DSC) was performed on nitro compound **2**. A melting endotherm at 184 °C was the only observable heat flow between 40 and 250 °C. This result helped establish the good stability of **2**.

Summary

The TFA solvent procedure and the solids addition procedure were two viable nitration processes for the conversion of **1** into **2**, but on the basis of safety data the TFA solvent process was chosen. Screening of the stability of nitro compound **2** using the CHETAH program indicated that further testing was warranted. The defining experimental safety data was from the ARC studies, which indicated an energetic exotherm for mixture A at fairly low temperatures, greatly disfavoring the solids addition process compared to mixture B. Experimental results from DSC and ARC did not indicate any stability problems for nitro product **2** at relevant temperatures. The safe use of TFA as a solvent for this nitration process should be noted as TFA has not been widely used for nitrations previously. The final process was safely implemented in a pharmaceutical pilot plant, producing a batch size of 23.5 kg of nitro compound **2**.

Experimental Section

General Procedures. All materials were purchased from commercial suppliers and used without further purification. CHETAH, version 7.0, 3rd ed., is a program from ASTM. The DSC experiment was performed on a TA modulated DSC model 2920 using modulated DSC analysis version 1.1A.

3-Acetyl-4,5-dichloro-1,2-(ethylenedioxy)-6-nitrobenzene (2) Made by the TFA Procedure in Pilot Plant Equipment. A 50-gal glass-lined reactor was charged with 22.3 kg (90.3 mol) of 3-acetyl-4,5-dichloro-1,2-(ethylenedioxy)benzene (**1**) followed by 33.0 kg of trifluoroacetic acid. The solution was cooled to 0−5 °C, and a slow sweep of nitrogen was maintained in the reactor. Slowly over 2 h 20 min, 5.49 L (117.6 mol) of 90% nitric acid was added to the solution. The reaction mixture reached a maximum temperature of 12 °C. The mixture was stirred for 1 h at 2−12 °C and then for 2 h at 19−21 °C. The mixture was cooled to 14 °C, and 112 kg of 3 °C tap water was added over 15 min. The mixture was stirred for 30 min with a final temperature of 12 °C. The solution was filtered through a Hastelloy Rosenmund filter, and the cake was washed with 2 × 30 kg of tap water followed by 2 × 12 kg of methanol. The material was dried by passing nitrogen through the cake for 72 h. The cake was discharged, yielding 23.5 kg (89%) of **2** as a light yellow solid: mp 182.4−185.3 °C; ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 3), 4.39 (s, 4); ^{13}C NMR (acetone-d_6) δ 31.45, 65.89, 66.24, 116.17, 120.11, 133.13, 137.53, 140.65, 141.86, 197.79; IR (KBr) 1715 cm^{-1}. Anal. Calcd for $C_{10}H_7NO_5Cl_2$: C, 41.12; H, 2.42; N, 4.80. Found: C, 41.10; H, 2.39; N, 4.65.

3-Acetyl-4,5-dichloro-1,2-(ethylenedioxy)-6-nitrobenzene (2) Made by the Solids Addition Procedure in 12-L Glassware. In a 12-L flask was placed 2.0 L of 90% nitric acid. The nitric acid was cooled, and over 1 h 40 min was added 1.0 kg (4.05 mol) of 3-acetyl-4,5-dichloro-1,2-(ethylenedioxy)benzene (**1**) while the reaction mixture was maintained at −22 to −15 °C. The reaction mixture was aged for 1 h, and then 5.0 L of tap water was added over 35 min, the temperature being kept below 11 °C. The mixture was aged for 1 h 10 min with a final temperature of 0 °C. The mixture was filtered, and the cake washed with 2 × 4 L of tap water. The cake was dried on drying trays in a forced-air oven at 43 °C overnight, yielding 1.12 kg (95%) of **2** as a light yellow solid, identical to **2** prepared above.

Accelerating Rate Calorimetry Experiments. All experiments were conducted in a titanium or Hastelloy C ARC bomb measuring the temperature and pressure over time with a sensitivity of 0.02 °C/min. The sample from Table 6, entry 1, was heated from 50 to 300 °C; entry 2 was heated from 35 to 200 °C; entry 3 was heated from 30 to 200 °C; and entry 4 was heated from 30 to 120 °C.

Reactive System Screening Tool Experiments. All experiments were heated from 20 to 130 °C at 0.25 °C/min. A glass reaction chamber, Teflon-coated stir bar, and Hastelloy thermocouple were used.

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