

Lab Development of the Synthesis of Green, New, and Innovative Nitrating Agent N-Nitrosaccharin for Potential Production Scale Nitration by Optimization, Scale-up, Risk Analysis, and Product Characterization

Arnaud Pierre Ehrsam

CHEMICAL DEVELOPMENT & PRODUCTION

EIA-FR

Advisor: Dr. Roger. Marti // In collaboration with **Katayev Group**

DESCRIPTION

Since the beginning of nitration route finding, until today, the most used and efficient nitration process has been using the mixed acids approach of nitric and sulfuric acid. This technique, although very efficient and cheap, generates important amounts of aqueous waste, difficult to treat, polluting, and remains a risk-taking approach to nitration. To move on, bring change, safety, and respect to humans and our planet, steps need to be taken to develop new nitration routes that lead to safe manipulation, and eco-friendly conditions. Recently, a nitration route using N-Nitrosaccharin as a nitrating agent was shown to be the most efficient, economical, and environmentally friendly pathway, for potential substitution according to research. However, the synthesis of N-Nitrosaccharin contradicted its green nature, as harmful conditions and reagents were being used.

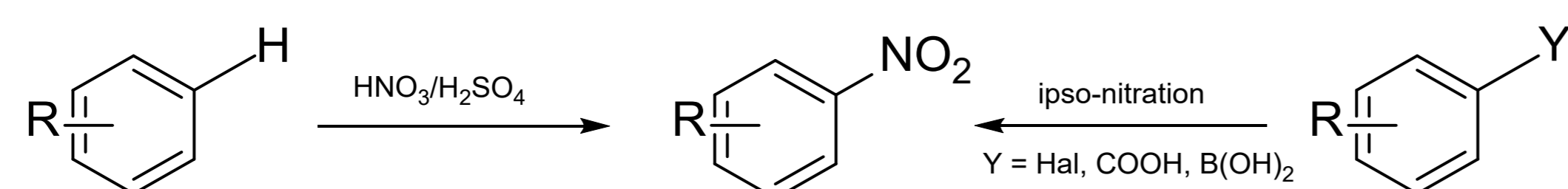


Figure 1. Classical nitration pathways

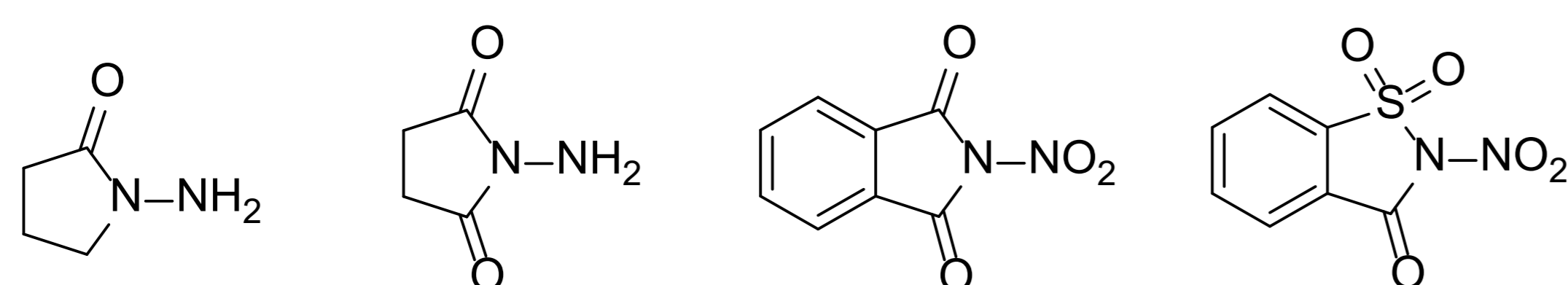


Figure 2. Novel nitrating agents

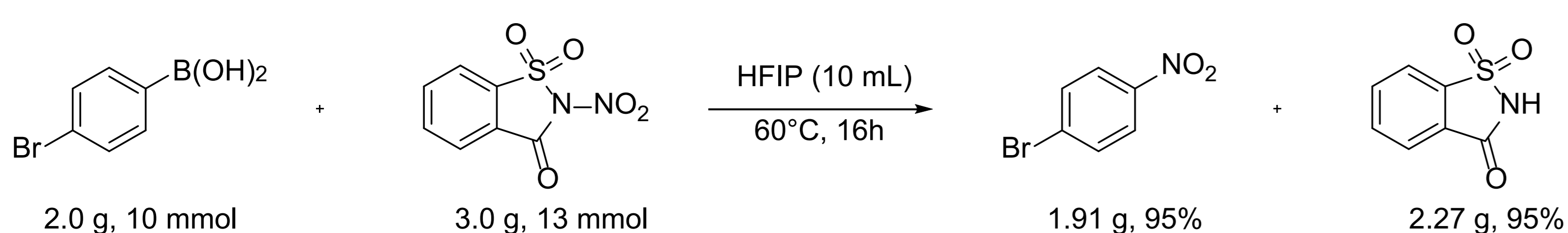


Figure 3. Proven nitrating efficiency using N-Nitrosaccharin

OBJECTIFS

Develop a process for the synthesis of N-Nitrosaccharin by respecting greenness of the process, chemical efficiency, and low costs, through:

1. Screening tests
2. Optimization
3. Scale-up
4. Risk analysis
5. Greenness

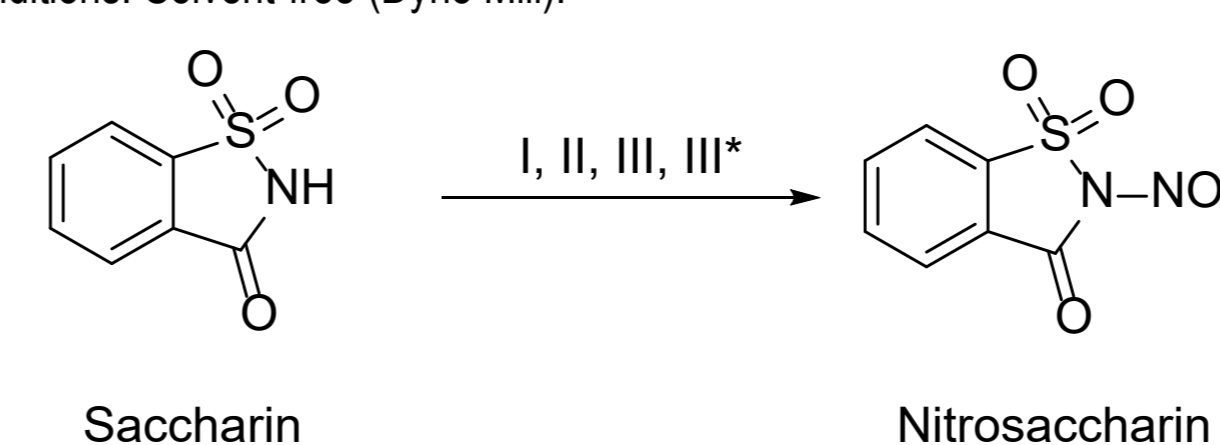
Studying the process and the product through:

1. Kinetic studies
2. Impurities and waste management
3. In-situ analysis
4. Calorimetric studies and stability tests

RESULTS

| Entry | Conversion [%] | Assay [%] | Yield [%] | PMI [-] | RME [%] | Green Score ¹ | Safety Remarks | EcoScale | DOZN |
|----------------|----------------|-----------|-----------|---------|---------|--------------------------|--|----------|------|
| 1 ^a | 88 | 89.3 | 76 | 23 | 8 | 4.7 | Large gas release | 78 | 5 |
| 2 ^b | 79 | 38.1 | 29 | 14 | 12 | 5.2 | Tf ₂ O complex manipulation | 51 | 3 |
| 3 ^c | 100 | 98.2 | 91.2 | 6 | 27 | 6.9 | - | 89 | 2 |
| 4 ^d | 100 | 96.2 | 82.0 | 6 | 25 | 6.9 | - | 83 | 2 |
| 5 ^e | 100 | 95.1 | 91.2 | 6 | 27 | 6.9 | Safest conditions with AcOH | 89 | 2 |
| 6 ^f | 100 | 99.0 | 95.9 | 5 | 32 | 6.7 | Safest conditions without AcOH | 90 | 1 |
| 7 ^g | 100 | 96.2 | 92.0 | 31 | 25 | 6.9 | - | 83 | 2 |
| 8 ^h | 46 | 90.0 | 65.7 | 5 | 22 | 7.1 | - | 74 | 1 |

¹Initial synthesis route using a mixture of HNO₃/Ac₂O, 0-21°C. ²2nd synthesis route using a mixture of NaNO₂/Tf₂O/AcOH in 25 mL of MeCN, 0-21°C. ³3rd synthesis route using a mixture of KNO₃/MSAA/AcOH in 25 mL of MeCN, 50°C. ⁴100g scale-up of Entry 3 in 250 mL of MeCN, 50°C. ⁵4th synthesis route with corrected order of addition (KNO₃ added last), in 75 mL of MeCN, 50°C. ⁶5th synthesis route without the use of AcOH, in 25 mL of MeCN, 35°C. ⁷Conditions: Same as Entry 4, but work-up was included in PMI and RME calculation. ⁸Conditions: Solvent-free (Dyna Mill).



I = Ac₂O, HNO₃, 0°C -> r.t
II = Tf₂O, NaNO₂, AcOH, 0°C -> r.t in MeCN
III = MSAA, KNO₃, AcOH, 50°C in MeCN
III* = MSAA, KNO₃, r.t, solvent-free

Figure 4. Optimization process leading to final conditions (III)



Figure 6. Initial reaction conditions (I)

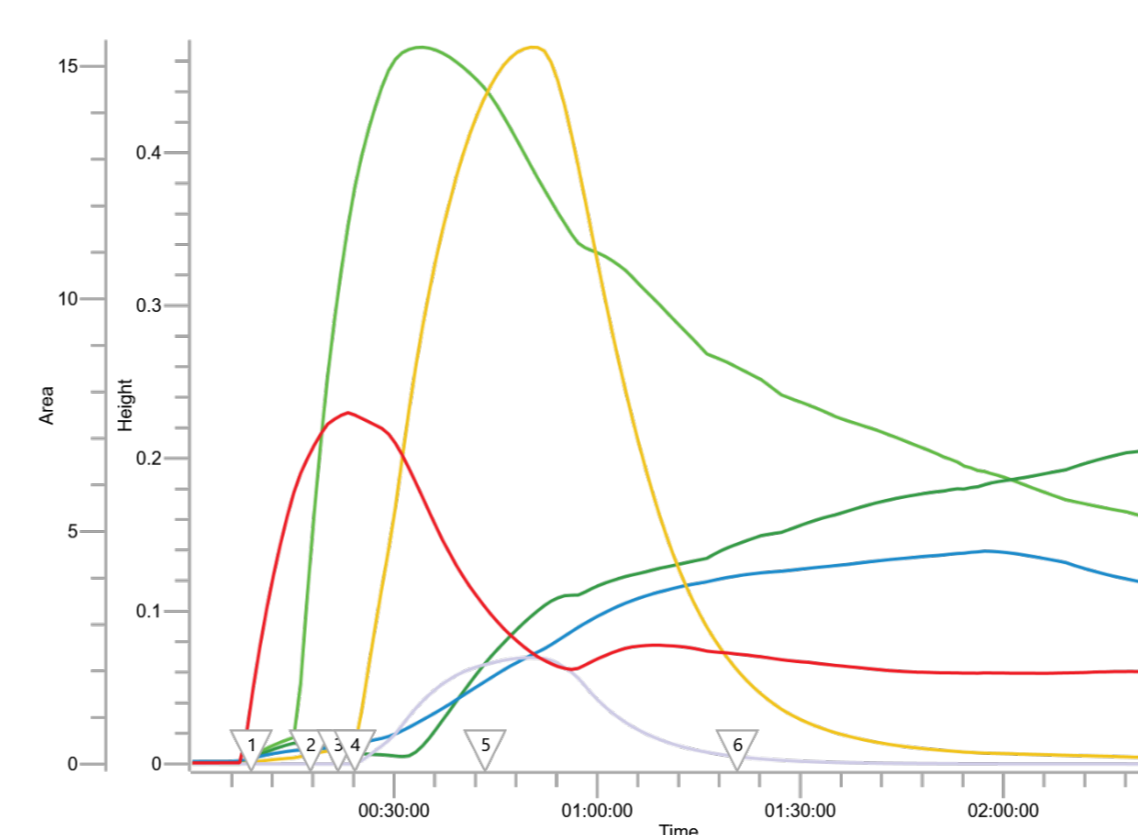


Figure 8. Reaction profile done using in-situ FTIR

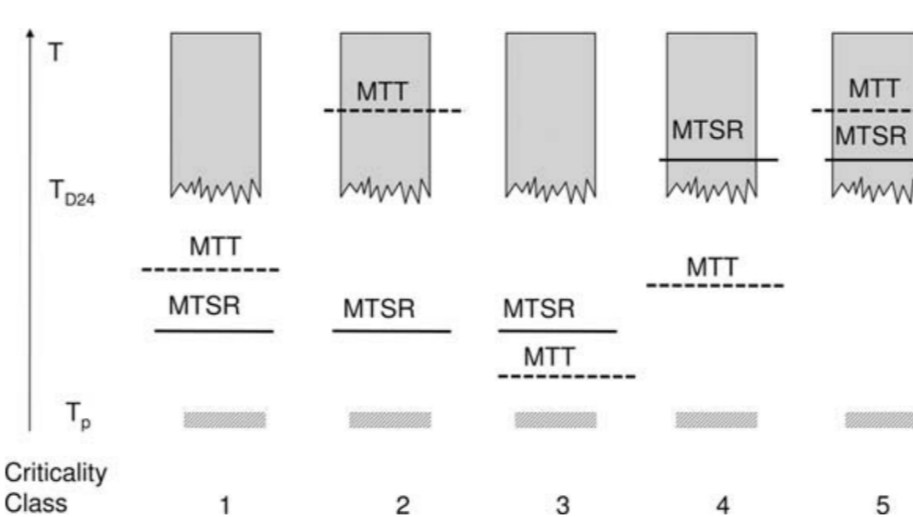


Figure 10. Criticality class of process (2)

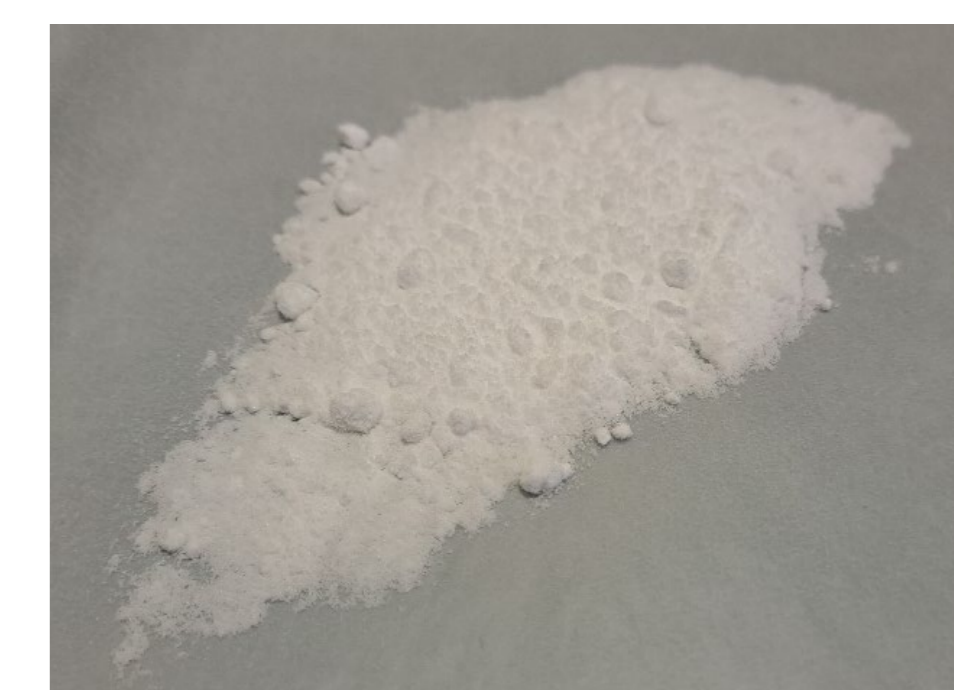


Figure 5. N-Nitrosaccharin



Figure 7. Optimal conditions and 100g scale-up (III)

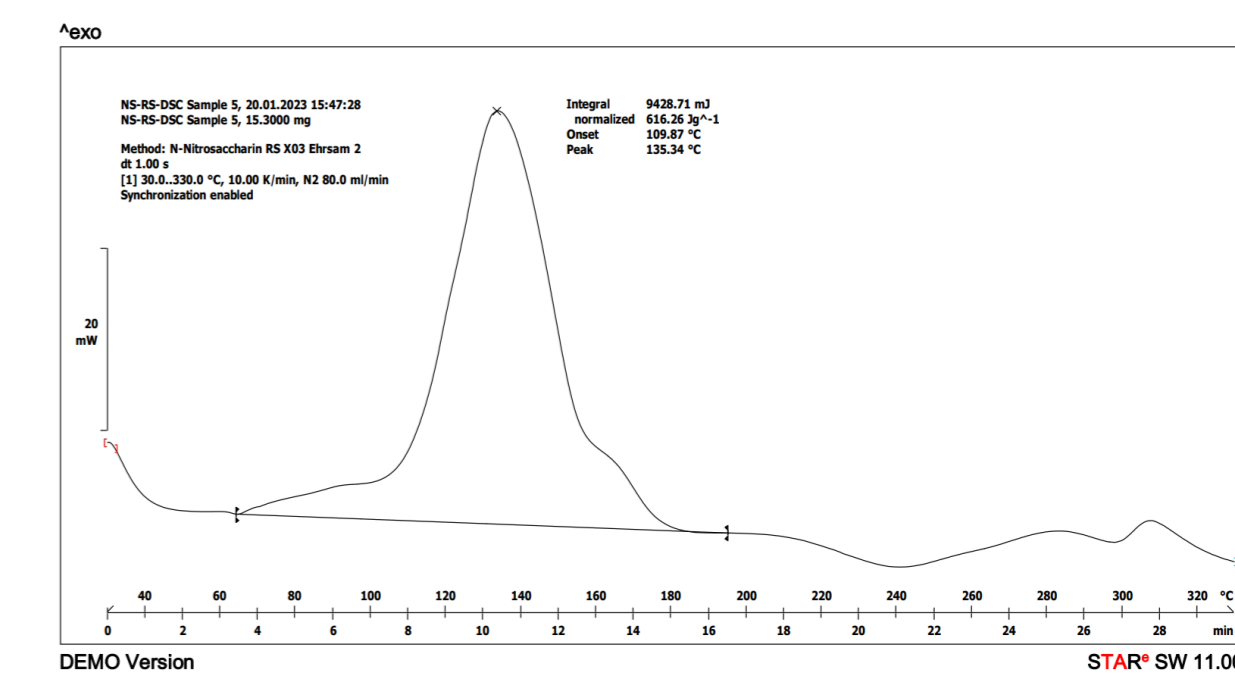


Figure 9. Reaction mixture decomposition temperature and profile

$$v = k * [\text{Saccharin}]^{0.6} * [\text{MSAA}]^{0.03} * [\text{KNO}_3]^{1.4} * [\text{AcOH}]^{0.4}$$

Figure 11. Process rate law

CONCLUSION

It is fair to state, that in terms of chemistry, greenness, and cost, this process has been successfully optimized and developed at lab scale. But a chemical process rarely sticks to lab scale, and the goal for industrialists is to commercialize a process that can generate revenue. During the synthesis, almost no exothermic behavior is to be reported, and if there is one, it's negligible, which means that a runaway that originates from the reaction itself is almost improbable. However, decomposition temperature of the reaction mixture in the first 30 minutes of the reaction is of 60°C if rounded down for a worst-case scenario situation. This means only 10°C separate reaction temperature to decomposition of the reaction mixture which is highly exothermic. At lab scale, this does not pose a problem, as heating and cooling is a fast process which allows easy control of runaway situations. However, in production scale, let's say pilot-lab scale, to take the "safest" production scale situation, a 600L reactor needs hours to heat and cool. This is a problem for the synthesis of N-Nitrosaccharin, but as was proved in this study, this process is capable of nitrating other substances, such as aliphatic secondary amides, cyclic secondary amines, and even benzene substituted molecules such as phenylboronic acid. As for N-Nitrosaccharin, there is no doubt it's an effective and interesting nitrating agent. As was presented in this report, synthesis of nitrobenzene using N-Nitrosaccharin in just MeCN was successful and simple. Of course, development of this process, and risk assessment will also need to be done to confirm that ipso-nitration using N-Nitrosaccharin is a possibility.