

Continuous-Flow Nitration of o-Xylene to 4-Nitro-o-Xylene: Process Intensification, Selectivity, and Safety Window Evaluation

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Received: 22 March 2026; Accepted: 16 April 2026; Published: 28 April 2026

Abstract:

4-Nitro-o-xylene (1,2-dimethyl-4-nitrobenzene, 4-NOX) is an important intermediate for agrochemicals, pharmaceuticals, and dyes, and is commonly prepared via nitration of o-xylene; however, conventional mixed-acid batch nitration suffers from limited regioselectivity, dinitro byproduct formation, equipment corrosion, and scale-up safety concerns associated with rapid heat release and gas evolution. Here we present a continuous-flow feasibility study for the synthesis of 4-NOX, benchmarking an aqueous nitric acid system against a sulfuric/nitric mixed-acid system in a microreactor platform with GC-based product analysis. In the nitric-acid-only process, reaction performance depended primarily on nitric acid equivalents, temperature, residence time, and mixing efficiency. Under the optimized conditions of 85 wt% HNO₃ (5.09 equiv) at 60 °C with an approximately 31.6 s residence time, o-xylene conversion was essentially complete, delivering a high fraction of mononitration products with 4-NOX as the major isomer (4-NOX 50.33%, 3-NOX 46.06%; typical 3-NOX:4-NOX $\approx$ 1:1.1–1:1.2), while dinitro formation remained low. By contrast, under mixed-acid continuous-flow conditions at 25 °C with staged sulfuric acid addition (1.3 equiv HNO₃), conversion remained incomplete (~46% o-xylene), accompanied by appreciable dinitro impurities (~7% total), indicating a limited ability to simultaneously achieve high conversion and suppress over-nitration within practical residence times. Overall, the study demonstrates that continuous-flow nitration using aqueous nitric acid enables rapid, controllable mononitration of o-xylene within seconds and offers a more promising route to 4-NOX than the mixed-acid approach in the explored window, while highlighting downstream quench/acid handling as a key consideration due to the higher nitric acid loading.

Keywords:

4-nitro-o-xylene, Continuous-flow Synthesis, Microreactor, Process Intensification, Regioselectivity, Nitric Acid, Reaction Safety

1. Introduction

4-Nitro-o-xylene (1,2-dimethyl-4-nitrobenzene, 4-NOX) is an important nitroaromatic intermediate used broadly in the manufacture of fine chemicals, pharmaceuticals, agrochemicals, and dyestuffs. [1] As a functionalized aromatic building block, 4-NOX is frequently positioned upstream of reductive steps (to the

corresponding aniline) and subsequent derivatization (e.g., acylation, sulfonylation, urea/carbamate formation, and further aromatic substitution), enabling access to diverse nitrogen-containing intermediates and performance molecules. [2] In industrial supply chains, the availability of such nitroaromatic intermediates directly impacts cost, quality consistency, and throughput of downstream production lines, particularly when isomer distribution and trace impurities influence hydrogenation behavior, catalyst lifetime, crystallization, and specification setting.³ Notably, 4-NOX is a recognized intermediate in routes to the herbicide pendimethalin, a widely used pre-emergence herbicide that supports weed control and crop productivity at global scale. [4] Beyond crop protection, nitro-substituted xylenes and their derived anilines also serve as building blocks in dye and pigment manufacturing as well as in pharmaceutical intermediate synthesis, illustrating the cross-sector relevance of robust, scalable access to 4-NOX. [5]

The predominant industrial approach to 4-NOX is electrophilic aromatic nitration of o-xylene, typically conducted in stirred tank reactors using mixed acid ($\text{HNO}_3/\text{H}_2\text{SO}_4$) or related acid systems. [6] However, conventional batch nitration suffers from well-known drawbacks. First, regioselectivity is inherently limited, leading to substantial co-formation of 3-nitro-o-xylene, which creates a separation burden and caps the practical yield of the target 4-NOX isomer. [1] Second, the strong dependence of nitrating strength on acid composition and local water balance can promote over-nitration (dinitro byproducts) and oxidative side reactions, complicating impurity control and reducing overall process robustness. Third, mixed acid systems are highly corrosive and generate large quantities of spent acid, creating challenges in materials selection, waste treatment, and sustainability metrics. [7] Finally and most critically, nitration is a strongly exothermic, fast reaction frequently accompanied by NO_x evolution; in batch vessels, scale-up can amplify heat-removal and mixing limitations, increasing the likelihood of local hot spots, rapid pressure rise, and thermal runaway—factors that are subject to strict regulatory scrutiny worldwide. [8] These combined limitations motivate the development of intensified manufacturing strategies that can provide improved controllability and intrinsic safety without sacrificing productivity.

Continuous-flow processing has emerged as a powerful platform for hazardous and highly exothermic reactions by operating with low reactive inventory, high surface-area-to-volume ratios, and precisely defined residence time and temperature histories. [9,10] In addition to improved heat and mass transfer, flow reactors can be operated under controlled back pressure to stabilize gas–liquid behavior and suppress uncontrolled boiling or gas disengagement, thereby improving dosing reproducibility and process stability. For nitration chemistry in particular, the ability to enforce fast and reproducible mixing while removing heat efficiently can be decisive for selectivity, because the earliest contact zone between the aromatic substrate and the nitrating agent largely determines the extent of over-nitration and the formation of hard-to-remove trace impurities. [11]

Within continuous manufacturing, microreactors and tubular reactors are complementary tools rather than competing choices. Microreactors provide extremely short mixing times and exceptional heat-transfer performance, making them especially suitable for the front-end of fast, strongly exothermic reactions where most heat release occurs immediately upon reagent contact. [12] Their industrial deployment, however, is often constrained by pressure drop and throughput when narrow channels are used exclusively, particularly when multiple stages or long

residence times are required. [13] In contrast, tubular (pipe/coil) reactors offer cost-effective holdup volume, straightforward scale-out by length/numbering-up, and robust heat exchange through jacketed or tempered designs, making them well suited for downstream “maturation” zones where reaction rates slow but hazard classification remains high and temperature control is still mandatory. [14]

In this work, Shanghai Hybrid-chem Technologies implements a hybrid continuous-flow architecture combining a microreactor front end with a tubular reactor section to balance mixing performance, reaction rate, intrinsic safety, and overall capital efficiency. The nitration of o-xylene features a sharp, highly exothermic initial stage that benefits from microreactor intensification, whereas the downstream stage—although less exothermic—remains a high-hazard transformation subject to stringent policy and permitting requirements; implementing the latter in tubular reactors ensures the reaction continuously resides within a high heat-transfer environment while keeping equipment investment controllable, thereby reducing barriers to industrial adoption. [15] Importantly, using a single microchannel reactor design alone is often insufficient to address the practical complexity of industrial nitrations. To overcome this, Shanghai Hybrid-chem Technologies developed the proprietary PT series microreactors: the P-type design enables markedly lower pressure drop than conventional microreactors and therefore facilitates straightforward series integration of multiple reactor blocks, while the T-type design incorporates enhanced mixing structures that improve mixing performance by approximately 20% at the cost of increased pressure drop. By combining P- and T-type units strategically, we maintained the overall pressure drop within the controllable range of silicon-carbide reactor hardware (below 1.5 MPa) while achieving high micromixing intensity, which in turn improved the microreactor outlet performance and enabled an efficient continuous-flow route to 4-NOX.

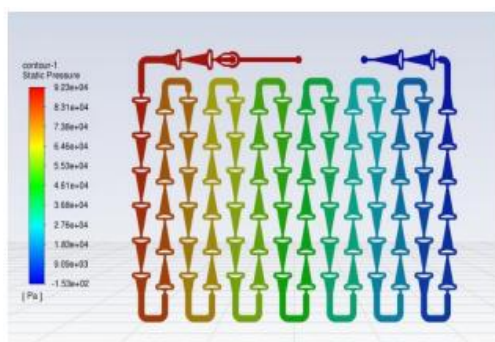


Figure 1. T-type Microreactor.

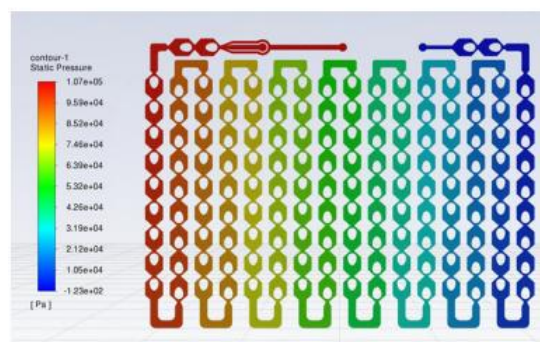


Figure 2. P-type Microreactor.

2. Experimental Section

All experiments were designed to develop a safe and controllable nitration process for converting o-xylene to mononitro-o-xylene isomers (3-NOX and 4-NOX) and to evaluate the feasibility of transferring the chemistry from batch to continuous flow. The study was initiated with bench-scale batch screening to establish baseline reactivity and operability, followed by continuous-flow trials to map key operating parameters (temperature, acid strength, equivalents, residence time, pressure/back-pressure, and mixing configuration), and finally by focused flow optimization leading to the selected best-condition experiment. Batch experiments were performed in a glass flask equipped with mechanical or magnetic stirring, an external temperature-control bath, and controlled addition capability. In a typical

batch run, o-xylene was charged to the reactor and brought to the target temperature, after which nitric acid (for the nitric-acid-only route) or pre-prepared mixed acid (for the $\text{HNO}_3/\text{H}_2\text{SO}_4$ route, with composition adjusted by adding water to set the targeted dehydration value) was introduced by dropwise addition at a controlled rate while maintaining temperature; where staged dehydration was evaluated, an additional stream of sulfuric acid was added after an initial nitration period to increase the dehydration value according to the planned schedule. After completion of addition, the reaction mixture was held for a predefined time under continued agitation, then quenched by controlled dilution/neutralization as per safety practice, and the organic phase was separated for analysis; selected samples were additionally washed with aqueous sodium bicarbonate solution to assess the effect of post-treatment on analytical profiles. Continuous-flow experiments were conducted on a modular microreactor platform consisting of independent feed delivery for o-xylene and acid, a temperature-controlled microstructured mixing/reaction module, an optional residence-time extension section (coil/tubing for “maturation”), a temperature-controlled cooling module, and a downstream back-pressure regulator; the full flow setup and connection scheme should be inserted as: Figure 1 (flow setup schematic showing feed tanks/pumps, microreactor module, optional tubular/coil section, cooling segment, and BPR/pressure measurement points), and representative reactor/mixer hardware images should be inserted as: Figure 2 (photographs of the microreactor modules and tubular/coil section used in this work). Prior to each flow run, the system was pressure-tested, flushed with compatible solvent, preheated/precooled to the setpoints, and stabilized at the target back pressure; reagent lines were primed to eliminate gas pockets, and flow rates were verified gravimetrically over a timed interval. For nitric-acid-only flow trials, aqueous nitric acid solutions of specified concentration (notably 65% and 85%) were fed against o-xylene at predefined equivalents, and the reaction temperature, residence time (set by total flow and reactor/hold-up volume), and back pressure were varied systematically; for mixed-acid flow trials, the initial mixed acid ($\text{HNO}_3/\text{H}_2\text{SO}_4/\text{H}_2\text{O}$) was prepared in advance to the desired initial dehydration value, delivered as a separate feed to the o-xylene stream, and a second sulfuric acid feed was introduced downstream (or at a defined junction) to raise the overall dehydration value in a staged manner, with the tubular section providing additional controlled residence time before quench and sampling. Product streams were collected only after reaching steady state (typically after multiple residence times), and sampling points and collection windows should be indicated as: Figure 3 (sampling strategy and residence-time definition, including locations for T1–T4 and pressure measurement).



Figure 3. Industrialized Microreactor.

All samples were analyzed by GC-FID using an Agilent 6890 with a DB-1 capillary column ($30\text{ m} \times 0.32\text{ mm} \times 0.5\text{ }\mu\text{m}$); the oven program, injector/detector temperatures,

carrier gas flow, and other parameters should be inserted as: Table 1 (GC method parameters used for quantification of o-xylene, 3-NOX, 4-NOX, and byproducts). Between experimental sets, the reactor was thoroughly flushed until baseline chromatograms were observed to prevent cross-contamination, and particular care was taken to manage gas evolution and flow stability by adjusting back pressure and ensuring temperature control during start-up, operation, and shutdown. This standardized sequence—from batch baseline experiments, to continuous-flow “touch” experiments for operability mapping, to structured flow optimization.

Table 1. Representative results across development stages for o-xylene nitration (GC area%, FID).

Entry	Stage	System	Key conditions (summary)	o-Xylene (%)	3-N OX (%)	4-N OX (%)	Dinitro total (%)	Others (%)	Note / purpose
1	Batch bench mark	Nitric acid only	95% HNO ₃ , 80 °C, addition completed; long hold (210 min)	30.04	15.56	24.79	0.00*	29.61	Shows batch can reach conversion but with many unidentified peaks; strong fuming/exotherm (LH050-2023 1130-1-7).
2	Batch bench mark (best mixed-acid conversion)	Mixed acid	60 °C, dehydration value 2.5, HNO ₃ 1.3 eq, two-step acid addition, 2 h	4.05	44.39	36.52	10.72	4.34	High conversion but significant dinitro; illustrates conversion-over-nitration coupling.
3	Flow screening	85% HNO ₃ only	60 °C, HNO ₃ 1.2 eq	72.52	12.47	15.01	0	0	Establishes that low equivalents limit conversion in flow.
4	Flow optimization (equivalent effect)	85% HNO ₃ only	60 °C, HNO ₃ 4.0 eq	7.75	38.22	50.26	1.43	2.2	Near-complete conversion; demonstrates equivalents as main “knob”.
5	Flow best condition	85% HNO ₃ only	60 °C, HNO ₃ 5.09 eq, residence time 31.6 s	0.09	46.06	50.33	1.13	2.4	Selected optimum: essentially full conversion with high mononitro fraction.
6	Flow bench mark (mixed-acid feasibility)	Mixed acid + staged H ₂ SO ₄	25 °C, initial mixed acid (65% HNO ₃ /98% H ₂ SO ₄ /H ₂ O), HNO ₃	46.69	22.85	20.19	7.04	3.23	Mixed-acid flow remains conversion-limited and forms dinitro.

			1.3 eq, dehydration value to 3.22, 6RT sampling						
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3. Results and Discussion

Initial batch experiments were carried out to establish a benchmark for o-xylene nitration and to identify the dominant constraints that typically govern stirred-tank operation. Under nitric-acid-only batch conditions, the reaction exhibited a strong temperature sensitivity and pronounced hazard characteristics: even exploratory trials based on literature guidance rapidly developed over-temperature/over-pressure behavior, indicating that heat removal and gas management are decisive for safe operation in a vessel environment. Consistent with this, the batch profiles showed that meaningful conversion was achieved primarily during the addition period, whereas post-addition conversion proceeded slowly, implying that effective generation/retention of the active nitrating species and local concentration control are critical. In mixed-acid batch nitration, conversion could be increased by raising dehydration strength and/or temperature, but these same levers also promoted dinitration and formation of additional impurity peaks, creating a persistent trade-off between conversion and selectivity. Overall, the batch benchmark highlights three intrinsic limitations: (i) mixing- and heat-transfer limits that lead to local hot spots and transient high nitrating strength during acid addition; (ii) an unfavorable coupling of conversion with over-nitration in mixed acid systems; and (iii) an operational safety bottleneck driven by fast kinetics, strong exotherm, and NO_x evolution, which becomes increasingly difficult to manage as scale increases. These observations motivated a shift to continuous processing to decouple conversion from selectivity and to establish a safer, more controllable operating window.

Continuous-flow trials began with conditions close to conventional practice to evaluate operability and define a stable baseline. Using 65 wt% HNO₃ in the microreactor platform, increasing temperature from ~30 to 90 °C led only to modest formation of mononitro products, with o-xylene remaining dominant in the product stream. Moreover, at higher temperatures the system pressure increased and gas behavior became more pronounced, consistent with nitric acid decomposition and NO_x generation, which can destabilize dosing and reduce effective nitrating strength. These results indicated that, under flow, 65% nitric acid was insufficient to drive the reaction to high conversion within the explored residence times, and that simply increasing temperature is not an effective lever because it simultaneously aggravates gas formation and operability. In contrast, switching to 85 wt% HNO₃ immediately improved conversion and established a practical temperature regime in which the microreactor could maintain stable operation, efficient heat removal, and controllable back-pressure behavior. This step was pivotal: it demonstrated that continuous flow can access an intensified nitration regime using aqueous nitric acid while keeping the process within a controllable thermal envelope.

After identifying 85% HNO₃ as the preferred oxidant strength for flow, the process was optimized primarily by varying nitric acid equivalents and residence time. At 60 °C, increasing HNO₃ equivalents systematically drove o-xylene conversion upward and shifted the product stream toward a high fraction of mononitration products. Once

the HNO_3 loading approached $\sim 4.5\text{--}5.0$ equivalents, conversion became essentially complete under steady-state operation. Subsequent residence-time studies showed that the reaction could be brought to near completion at residence times on the order of tens of seconds: at approximately 31.6 s, o-xylene was reduced to trace level (0.09% by GC area), while the product distribution remained dominated by the two mononitro isomers with only minor dinitro contribution. Under these optimized conditions (85% HNO_3 , ~ 5.09 equiv, 60°C , ~ 31.6 s), the GC area percentages reached 4-NOX 50.33% and 3-NOX 46.06%, corresponding to a typical 3-NOX:4-NOX ratio of $\sim 1:1.1\text{--}1:1.2$ and a combined mononitro fraction above 96%. Importantly, the ability to realize high conversion and high mononitro selectivity within seconds underscores the core benefit of flow processing for this chemistry: by sharply reducing characteristic mixing times and providing superior heat transfer, the microreactor limits the lifetime and spatial extent of highly aggressive local nitrating zones that otherwise drive over-nitration and degradation.

To directly compare with conventional practice, a mixed-acid continuous-flow strategy was evaluated using staged sulfuric acid addition to increase dehydration value while attempting to suppress dinitro formation. Although this approach reduced the residence-time penalty relative to batch and maintained the reaction under continuous heat-transfer conditions, the mixed-acid flow runs still exhibited the same fundamental coupling observed in batch: achieving high conversion required higher effective nitrating strength (higher dehydration value), but this simultaneously increased over-nitration. Under the tested conditions (25°C , total dehydration value ~ 3.22 , HNO_3 1.3 equiv), conversion remained incomplete with $\sim 46\%$ o-xylene remaining, while dinitro impurities reached $\sim 7\%$ total by GC area. These results indicate that, within practical residence times, mixed-acid nitration struggles to satisfy both objectives simultaneously (high conversion and low dinitro), even when implemented in continuous mode. In addition, the product ratio remained close to $\sim 1.1:1$ (3-NOX:4-NOX), giving a comparatively lower 4-NOX fraction than desired for an intermediate-focused process.

A key outcome of this work is that the nitric-acid-only route—while attractive from a selectivity and impurity standpoint under flow—cannot be translated straightforwardly to stirred-tank operation. In batch, implementing the same intensified nitration regime faces multiple barriers: (i) insufficient heat removal capacity during acid–aromatic contact leads to rapid temperature excursions; (ii) gas evolution and NO_x release complicate stoichiometry, mass transfer, and pressure control, especially during addition; (iii) local concentration gradients during addition create transient, highly reactive microenvironments that amplify side reactions and create inconsistent impurity profiles; and (iv) the larger reactive inventory in a vessel increases the consequence of any loss of temperature control. These constraints make it difficult to safely reach the combination of high nitrating strength and tight residence-time control required for rapid, selective mononitration. Continuous flow addresses each of these bottlenecks directly: the reaction inventory is minimized, heat transfer is intensified, mixing is reproducible, and residence time is precisely defined. Consequently, the nitric-acid-only continuous-flow process achieves a product distribution and overall mononitration performance that is substantially better than what is typically achievable in batch, effectively delivering a continuous outcome that exceeds the conventional batch “theoretical” expectation for isomer distribution and impurity suppression under practical operating constraints.

From a safety perspective, the flow platform demonstrated clear advantages for this strongly exothermic nitration: the most hazardous heat-release zone is confined to a small microreactor volume with high heat-transfer area, and downstream cooling further stabilizes the effluent before collection. From an efficiency standpoint, the process compresses reaction time from the order of minutes–hours (typical batch holding and post-addition completion) to seconds, enabling high space–time productivity. The data further suggest that mixing quality is a decisive variable, as changes in flow rate and residence time influenced not only conversion but also the 3-NOX/4-NOX ratio, consistent with the nitration being sensitive to local reaction conditions established during the earliest mixing period. Taken together, these results support the conclusion that continuous-flow nitration using aqueous nitric acid constitutes the most feasible and industrially compelling pathway explored in this study, while mixed-acid flow nitration remains challenged by conversion–selectivity trade-offs and dinitro formation. The remaining development focus for scale-up is therefore not reaction feasibility but rather downstream handling—quench strategy, acid recovery or neutralization, and waste minimization—required to economically support operation at elevated nitric acid equivalents.

At present, this research outcome has been successfully tested and put into operation on the following industrial equipment.

4. Conclusions

In this study, we established a practical development path from batch benchmarking to continuous-flow feasibility screening and process-window optimization for the nitration of *o*-xylene to 4-nitro-*o*-xylene (4-NOX). Batch trials confirmed the well-known limitations of stirred-tank nitration for this substrate: strong exothermicity and gas evolution create scale-up safety constraints, while mixed-acid conditions impose an inherent trade-off between conversion and over-nitration, leading to dinitro byproducts and a heavy downstream separation burden. Continuous-flow operation, by contrast, enabled precise control of mixing, heat removal, and residence time, allowing the reaction to be driven rapidly and reproducibly under a significantly safer reactive inventory.

Among the evaluated routes, the nitric-acid-only strategy proved clearly superior within the explored conditions. The best-performing continuous-flow conditions were obtained by directly mixing 99% *o*-xylene with 85 wt% aqueous nitric acid in a microreactor at 60 °C, using 5.09 equivalents of HNO₃ and a residence time of approximately 31.6 s, followed by rapid cooling to ~20 °C. Under these conditions, *o*-xylene was essentially fully consumed (0.09% residual by GC area), and the product stream consisted predominantly of mononitro isomers with 4-NOX as the major component (4-NOX 50.33%, 3-NOX 46.06%; typical 3-NOX:4-NOX ≈ 1:1.1–1:1.2) and only minor dinitro formation. In contrast, mixed-acid continuous-flow experiments, even with staged sulfuric acid addition (overall dehydration value ~3.22, 1.3 equiv HNO₃ at 25 °C), remained conversion-limited and produced appreciable dinitro impurities, indicating a lower feasibility for achieving both high conversion and impurity suppression within practical residence times.

The significance of this work is twofold: first, it demonstrates that aqueous nitric acid nitration—often impractical to intensify safely in batch—can be translated into an efficient and controllable continuous-flow process, delivering mononitration performance beyond what is typically achievable under vessel-based constraints;

second, it provides an industrially relevant rationale for hybrid reactor design in highly exothermic chemistry, where the microreactor front end addresses the most hazardous, mixing-sensitive heat-release zone and downstream continuous equipment maintains safety and cost-effective residence time. Future development will focus on integrated downstream processing (quench design, phase separation, acid recovery/recycle, NO_x management, and waste minimization) and on further tuning of mixing and hydrodynamics to improve the 4-NOX/3-NOX ratio and overall process economics, supporting scalable manufacturing of 4-NOX as an important intermediate for agrochemical and pharmaceutical value chains.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

This work was supported by the Key Science and Technology Program of the Ministry of Emergency Management of the People's Republic of China, Grant/Award Numbers: 2024EMST060601.

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