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Supporting Information

for

Continuous-flow-enabled intensification in nitration processes: a review of technological developments and practical applications over the past decade

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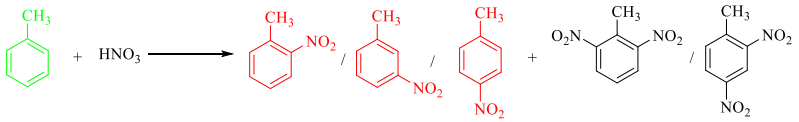
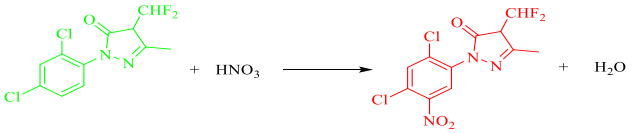
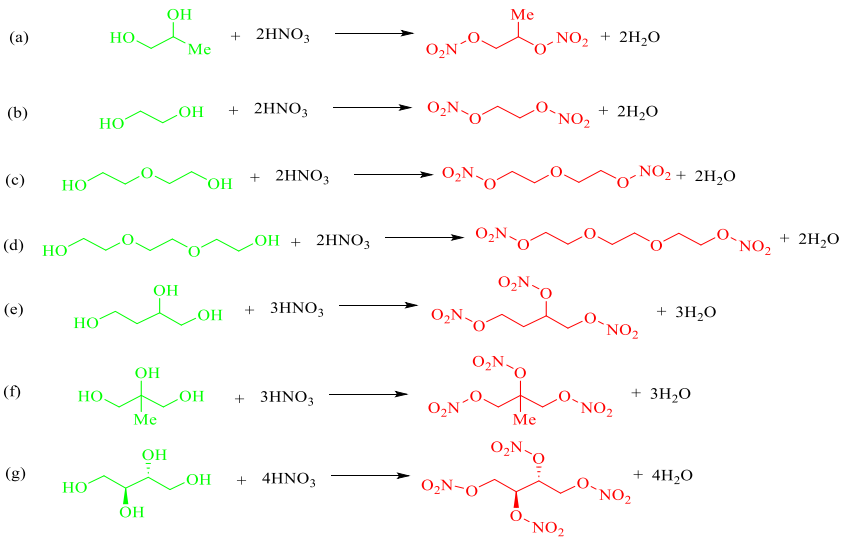
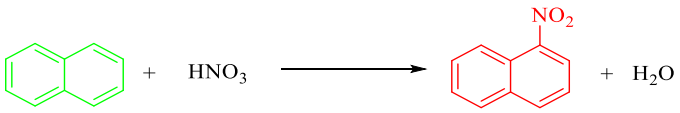
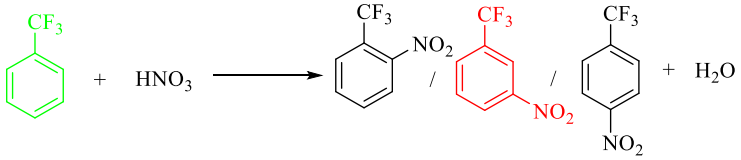
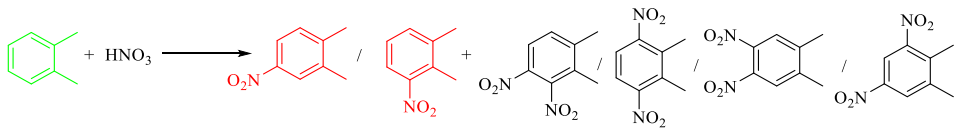
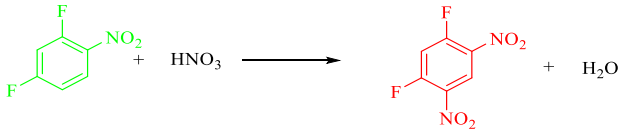
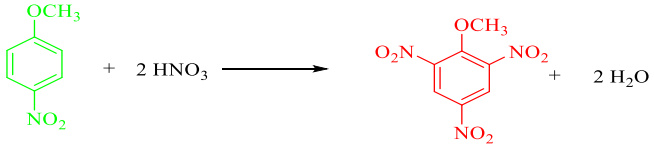
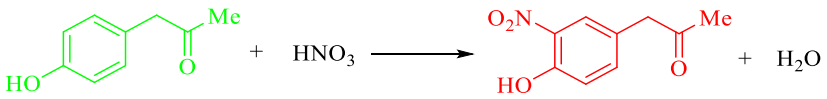
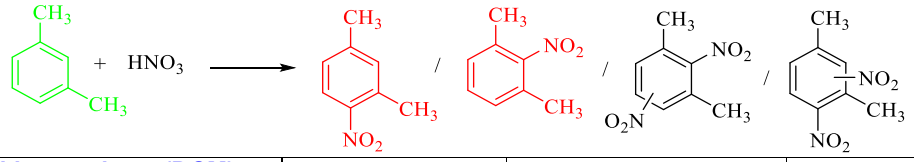
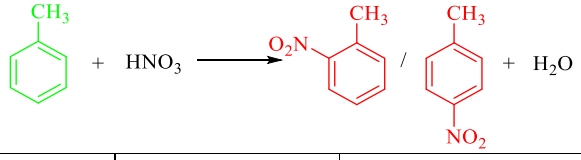
A complete table of developed continuous-flow nitration processes over the past decade (Table S1) and the nomenclature used in this review

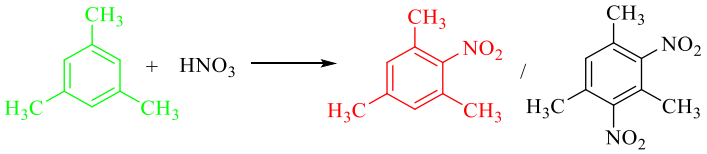
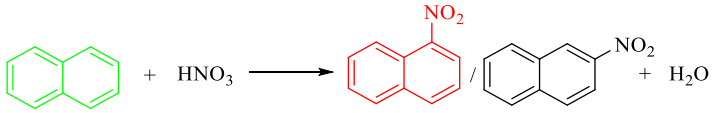
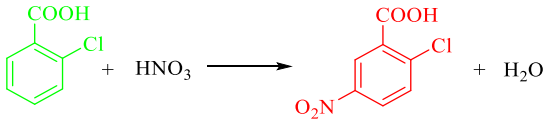
Table S1: Developed continuous-flow nitration processes over the past decade.

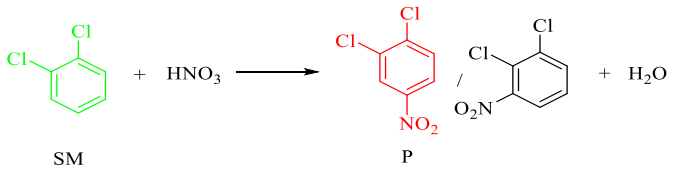
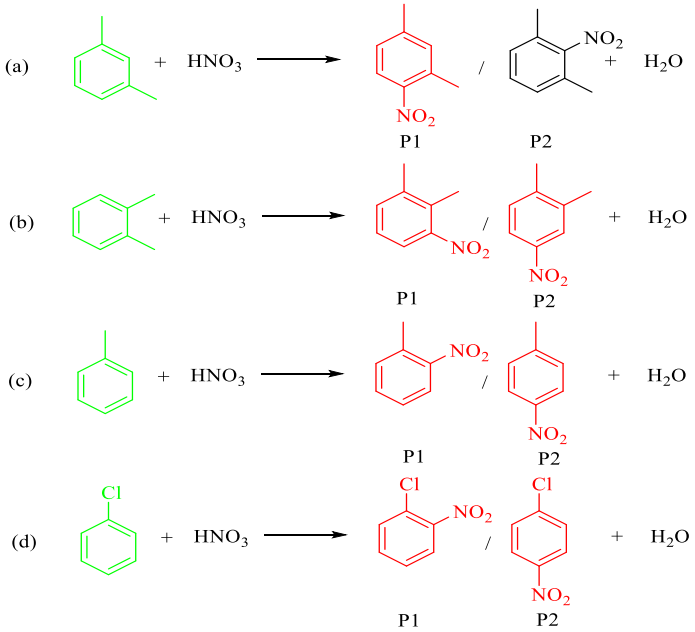
Sources	Reaction Scheme			
	Scope of process parameters research	Nitration substrates/ nitrating reagents	Analysis methods and results	Reactor forms
Wang, J. C. et al (2024) [1]				
	Solvent-free *T*=0-60 °C *M-ratio*(N/SM)=1.0-2.0 w_{AA}(%)=0-80% *t*= 60-180 s	Aromatic compounds /HNO_3-Ac_2O	**DoE** Solvent-free *T*=30 °C *M-ratio*(N/SM)=1.5 *w*AA(%)=65% *t*= 120 s **Yield=99.21%**	316L SS tubular reactor (ID, 0.8 mm; OD, 1.6 mm)
Cao, J. Y. et al (2024) [2]				
	1,2-dichloroethane(DCE) SM/DCE=1/5 w/w *M-ratio*(N/S)=1/8-1/2 *M-ratio*(N/SM)=1.05-2.0 *T*=40-70 °C *t*=25.7 s- 90.0 s	Aromatic compounds /Fuming HNO_3-Fuming H_2SO_4	**OFAT** Solvent DCE SM/DCE=1/5 w/w *M-ratio*(N/S)=1/6 *M-ratio*(N/SM)=1.1 *T*=60 °C *t*=30 s **Yield=97%**	Hastelloy(HC276) chip microreactor (a three-layer structure of 2 heat transfer layers and a reaction layer)
Mittal, A. K. et al (2023) [3]				
	Solvent-free/H_2SO_4 (a) *T*=15 °C, *t*=1-2 min, *M-ratio*(N/SM)=3-5, 12.7 M HNO_3 (HNO_3/H_2SO_4/H_2O = 51/43/6), Neat SM	Aliphatic compound/HNO_3-H_2SO_4	**OFAT** Solvent-free/H_2SO_4 (a)*T*=15 °C, *t*=1 min, *M-ratio*(N/SM)=5 12.7 M HNO_3 (HNO3/H_2SO_4/H2O=51	PFA tubular reactor (ID, 1 mm; OD, 1/16 inch; IV, 2 mL)

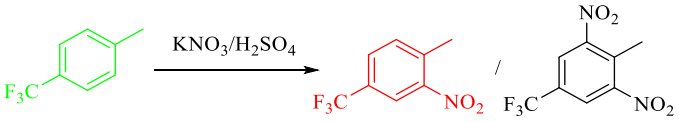
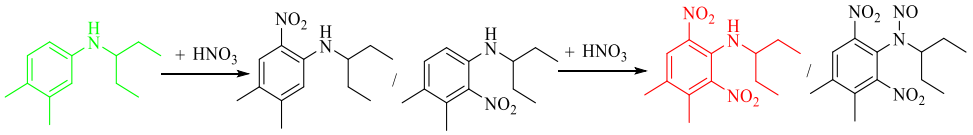
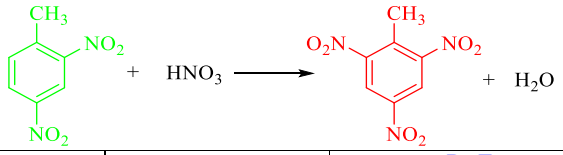
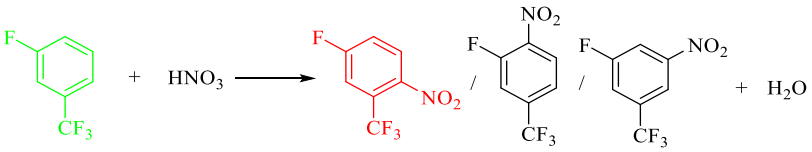
	(b) *T*=20-30 °C, *t*=1-2 min, *M-ratio*(N/SM)=3~4 12.7 M HNO_3(HNO_3/H_2SO_4/H_2O = 51/43/6), Neat SM (c) *T*=10-40 °C, *t*=1 min, *M-ratio*(N/SM)=3-4 12.7 M HNO_3 (HNO_3/H_2SO_4/H_2O=51/43/6) Neat SM (d) *T*=10-45 °C, *t*=1 min, *M-ratio*(N/SM)=3-5 12.7 M HNO_3 (HNO_3/H_2SO_4/H_2O=51/43/6) Neat SM (e) *T*=10 °C, *t*=1-2 min, *M-ratio*(N/SM)=5-6 12.7 M HNO_3 (HNO_3/H_2SO_4/H_2O=51/45/4) Neat SM (f) *T*=30-80 °C, *t*=1-2 min, *M-ratio*(N/SM)=6 2.0 M SM (95% H_2SO_4) Neat HNO_3(95%) (g) *T*=60-80 °C, *t*=1-2 min, *M-ratio*(N/SM)=6-8 1.7 M SM (95% H_2SO_4) Neat HNO_3(95%)		/43/6) Neat SM **Yield=93%** (b)*T*=30 °C, *t*=1 min, *M-ratio*(N/SM)=4 12.7 M HNO_3 (HNO_3/H_2SO_4/H_2O=51 /43/6) Neat SM **Yield=95%** (c)*T*=30 °C, *t*=1 min, *M-ratio*(N/SM)=4 12.7 M HNO_3 (HNO_3/H_2SO_4/H_2O=51/ 43/6) Neat SM **Yield=96%** (d)*T*=45 °C, *t*=1 min, *M-ratio*(N/SM)=5 12.7 M HNO_3 (HNO_3/H_2SO_4/H_2O=51 /43/6) Neat SM **Yield=95%** (e)*T*=10 °C, *t*=1 min, *M-ratio*(N/SM)=6 12.7 M HNO_3 (HNO_3/H_2SO_4/H_2O=51 /45/4) Neat SM **Yield=90%** (f)*T*= 80 °C, *t*=1 min, *M-ratio*(N/SM)=6 2.0 M SM (95% H_2SO_4) Neat HNO_3(95%) **Yield=94%** (g)*T*=80 °C, *t*=1 min, *M-ratio*(N/SM)=8 1.7 M SM (95% H_2SO_4) Neat HNO_3(95%) **Yield=96%**	
Xu, F. et al (2023) [4]				
	1,2-dichloroethane(DCE) SM/DCE=1/4 M/M *M-ratio*(N/SM)=0.8-2.0 *T*=30-50 °C *t*=10-120 s H_2SO_4 strength=74%-82%	Aromatic compounds / Fuming HNO_3-H_2SO_4	**OFAT** Solvent DCE SM/DCE=1/4 M/M *M-ratio*(N/SM)=1.2 *T*=30 °C *t*=120 s H_2SO_4 strength=74% **Yield=94.96%**	Teflon tubular reactor (ID, 0.8 mm; OD, 1.6 mm)
Guo, S. et al (2023) [5]				

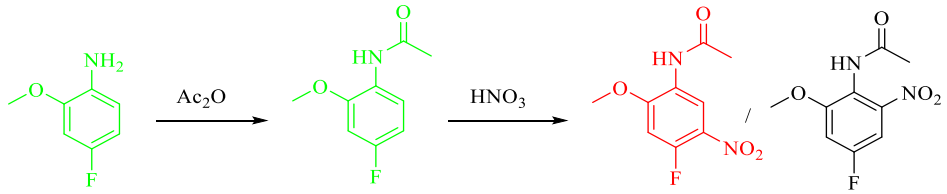
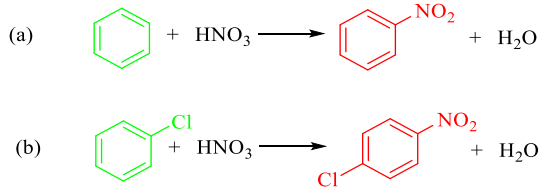
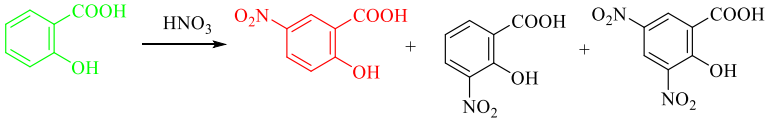
	Continuous-flow System A **Solvent-free** *M-ratio*(N/S)=0.78 *T*=10-20 ºC *t*=0-30 s Conc.(H_2SO_4) =86%-91% *M-ratio*(N/SM)=1.0-1.6 **Continuous-flow System B** **Solvent-free** *M-ratio*(N/S)=0.71-0.78 *M-ratio*(N/SM)=1.0-1.8 *T*=20-50 ºC *t*=0-30 s Conc.(H_2SO_4) =86%-93%	Aromatic compounds / Fuming HNO_3-H_2SO_4	**OFAT** **Continuous-flow System A** Solvent-free *M-ratio*(N/S)=0.78 *T*=20 ºC *t*=28 s Conc.(H_2SO_4) =91% *M-ratio*(N/SM)=1.2 **Conv.=22%** Notes: Not the final optimized result **Continuous-flow System B** Solvent-free *M-ratio*(N/S)=0.71 *M-ratio*(N/SM)=1.5 *t*=30 s **Conv.=100%**	**Continuous-flow System A** 316L SST T-mixer(ID, 3.3 mm)+PTFE tubular reactor(ID, 1mm) **Continuous-flow System B** Hastelloy(HC276) chip microreactor (a three-layer structure of 2 heat transfer layers and a reaction layer)
Guo, S. et al (2023) [6]				
	Solvent-free *Q*=20-60 mL/min Conc.(HNO_3)=88%-98% *M-ratio*(N/SM)=2-6 *T*=283-323 K *t*=0-60 s	Aromatic compounds / HNO_3	**OFAT** Solvent-free *Q*=60 mL/min *Conc.*(HNO_3)=94% *M-ratio*(N/SM)=3.6 *T*=323 K *t*=9 s **Conv.=100%**	Hastelloy heart-shaped chip microreactor
Guo, S. et al (2023) [7]				
	H_2SO_4 **Strategy 1-T-micromixer** *Re*=12.7-45 d_i=1.2-1.0 mm *T*=318-333 K *t*=0-36 s *M-ratio*(N/SM)=1.1 *M-ratio*(S/SM)=6 **Strategy 2-Heart-shaped microreactor** *Re*=58-204 *T*=318-333 K *t*=0-12 s *M-ratio*(N/SM)=1.1 *M-ratio*(S/SM)=6 *w*(H_2SO_4)=93%-98%	Aromatic compounds / HNO_3-H_2SO_4	**OFAT** **Strategy 1-T-micromixer** Solvent H_2SO_4 *T*=333 K *t*=36 s *M-ratio*(N/SM)=1.1 *M-ratio*(S/SM)=6 **Conv.=35%** **Strategy 2-Heart-shaped microreactor** Solvent H_2SO_4 *T*=333 K *t*=45 s *M-ratio*(N/SM)=1.1 *M-ratio*(S/SM)=6 **Conv.=98.5%**	PTFE tubular reactor(ID 1.2 mm/1.6 mm/2 mm)+Hastelloy heart-shaped chip microreactor
Mittal, A. K. al (2023) [8]				

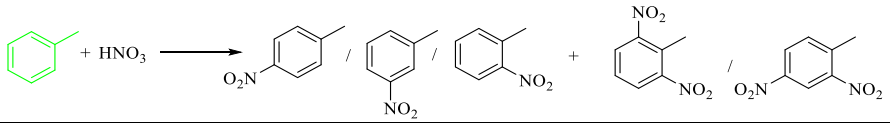
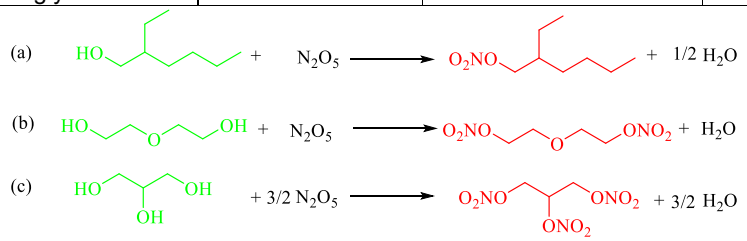
	H_2SO_4 Conc.(H_2SO_4-dissolving SM)=95%-98% 69% HNO_3 in 98% H_2SO_4 *M-ratio*(N/SM)=2.5-3 *T*=60-100 ºC *t*=0.5-5 min	Aromatic compounds / HNO_3-H_2SO_4	**OFAT** Solvent H_2SO_4 *T*= 80 ºC *t*=2.5 min *M-ratio*(N/SM)=2.5 Conc.(H_2SO_4-dissolving SM)=98% **HPLC purity=98%**	PFA tubular reactor (ID, 1 mm; OD, 1/16 inch; IV, 2 mL)
Petho, B. et al (2022) [9]				
	Dichloromethane (DCM) /AcOH *M-ratio*(N/SM)=1.025-1.1 *T*=25-45 ºC *t*=5-60 s *Q*=1-6 mL/min	Aromatic compounds / HNO_3-HAc	**OFAT** Solvent DCM/AcOH *M-ratio*(N/SM)=1.025-1.1 *T*=35-45 ºC *t*=10-60 s *Q*=1-6 mL/min **Conv.(max)=~100%** Note: Parameter adjustment for the actual production needs	Glass chip microreactor
Guo, S. et al (2022) [10]				
	Dichloromethane (DCM) SM/DCM=1/1 v/v **Stragety 1-Mixed acid** H_2SO_4 content=70-98 wt% HNO_3 content=70-98 wt% *M-ratio*(S/N)=0.8-2.33 *M-ratio*(N/SM)=1.2-2 *T*=20-50 ºC *t*=1 min **Stragety 2-HNO_3+H_2SO_4** H_2SO_4 content=80-90 wt% HNO3 content=90-98 wt% *M-ratio*(N/SM)=2-3.2 *T*=10-40 ºC *M-ratio*(S/SM)=1.5-2 *t*=0-120 s	Aromatic compounds / HNO_3-H_2SO_4	**OFAT** Solvent DCM SM/DCM=1/1 v/v **HNO_3+H_2SO_4(two-step mononitration)** H_2SO_4 content=80 wt% HNO_3 content=98 wt% *M-ratio*(N/SM)=2.4 *T*=40 ºC *M-ratio*(S/SM)=2 *t*=104 s **Conv.=99.5%** **Sel.(2,4-nitro)=83.8%** **Sel.(2,6-nitro)=15.2%**	Hastelloy(HC276) chip microreactor(the reaction layer comprises 36 heart-shaped cells)
Fu, G. et al (2022) [11]				
	Solvent-free *Q*=10-60 mL/min *T*=40-60 ºC *t*=2.2-5.1 min *M-ratio*(N/SM)=1-1.4	Aromatic compounds / HNO_3-H_2SO_4	**OFAT** Solvent-free *Q*=60 mL/min *T*=45 ºC *t*=2.2 min *M-ratio*(N/SM)=1.2 **SPY=1.36 $g \cdot L^{-1} \cdot s^{-1}$**	Hastelloy chip reactor(the channels were made of 1/4 in o.d hastelloy)

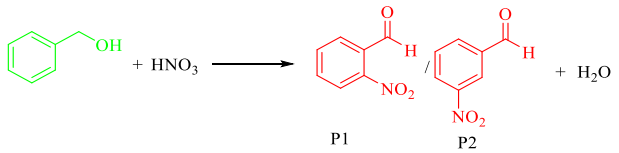
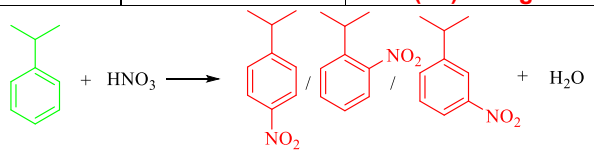
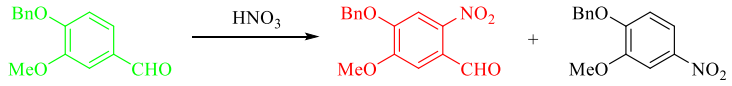
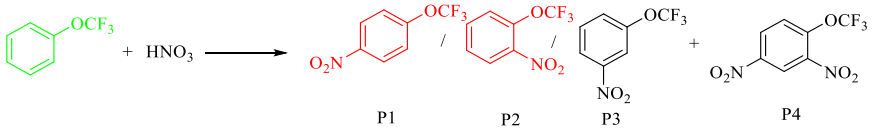
Guo, S. et al (2022) [12]				
	Dichloromethane(DCM) SM/DCM=1/1 v/v **Stragety 1-Mixed acid** Solvent type=EA/DCM/CS_2 /cyclohexane/None H_2SO_4 content=51-71 wt% *M-ratio*(S/N)=0.6-3 *M-ratio*(N/SM)=0-5.9 *T*=20-60 ºC *Q*=20-70 mL/min *t*=30 s **Stragety 2-HNO_3** *t*=30 s *T*=40 ºC *Q*=60 mL/min *M-ratio*(N/SM)=1-4 **Stragety 3-HNO_3+Mixed acid** H_2SO_4 content=60-90 wt% *M-ratio*(N/SM)=1.2-3.5 *T*=35-45 ºC *M-ratio*(S/SM)=0-1.7 *t*=0-60 s	Aromatic compounds / HNO_3 &HNO_3-H_2SO_4	**OFAT** Solvent DCM SM/DCM=1/1 v/v **Stragety 1-Mixed acid** *M-ratio*(S/N)=0.6 *M-ratio*(N/SM)=4.5 *T*=60 ºC **Yield=94.7%** **Impurtiy=4.4%** **Stragety 2-HNO_3** *M-ratio*(N/SM)=3 *T*=40 ºC **Yield=93.17%** **Impurtiy=0.8%** **Stragety 3-HNO_3+Mixed acid** *M-ratio*(S/N)=0.6 *M-ratio*(N/SM)=2.6 *T*=60 ºC *t*=60 s **Conv.=99.8%** **Yield=95%** **Purity=97%** **Throughput=1.88 kg/h**	Hastelloy (HC276) chip microreactor(the reaction layer comprises 36 heart-shaped cells)
Mule, G. M. et al (2022) [13]				
	N/A	Aromatic compounds / HNO_3	**OFAT** **I** The glass reactor configuration 2 CSTRs(1 L) in parallel+1 CSTR(2 L) **Production=148 kg/d** **II** The SS316L reactor configuration 2 CSTRs(2 L) in series **Production=218 kg/d** **III** Multipoint dosing 3 CSTRs(3 L/5 L/7 L) in series **Production=522 kg/d**	CSTR flow reactor
Sacher, S. et al (2022) [14]				
	H_2SO_4 Q_{SM}=0.4-1 mL/min Q_A=0.4-1 mL/min T=0-35 ºC	Aromatic compounds / HNO_3-H_2SO_4	**DoE** **N/A**	Split and recom-bine cascade mixer (Cascade Mixer 06)

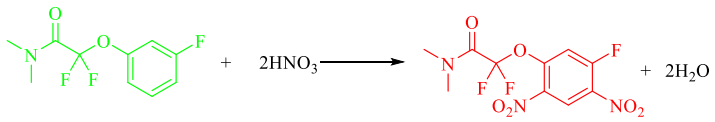
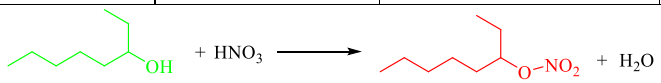
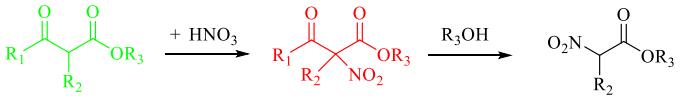
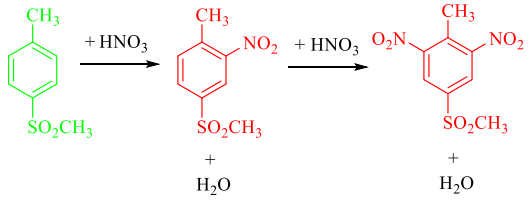
Lan, Z. et al (2021) [15]	 SM P			
	Solvent-free **ETFE tubular reactor** Conc. (SM, organic phase) =25-100% *T*=10-60 ºC *t*=0-200 s *M-ratio*(N/SM)=0~2 *M-ratio*(S/N)=4 **Micropacked-bed reactor** Conc. (SM, organic phase) =25-100% *t*=0-36 s *M-ratio*(N/SM)=0~2 *M-ratio*(S/(SM+P))=4	Aromatic compounds / HNO_3-H_2SO_4	**OFAT** ETFE tubular reactor Solvent-free *T*=40 ºC *t*=200 s *M-ratio*(N/SM)=1.1 *M-ratio*(S/N)=4 **Conv.=98.52%** **Sel.=89.02** **STY=0.0693 g/(L·s)** Micropacked-bed reactor Solvent-free *T*=30~70 ºC (Adiabatic) *t*=5 s *M-ratio*(N/SM)=1.1 *M-ratio*(S/N)=13.2 **Conv.=100%** **Sel.=88.97%** **STY=0.4382 g/(L·s)**	ETFE tubular reactor(ID 0.75 mm, OD 1.60 mm)/316L tubular reactor(ID 4mm, OD 6mm)/316L micropacked-reactor(ID 4mm, OD 6mm, packed with 0.177-0.250 mm/ 0.350-0.500 mm/0.500-0.710 mm glass beads)
Sagandira, M. B. et al (2021) [16]	 P1 P2			
	Reaction (a) **Solvent-free** **PTFE tubular reactor** Ultrasonic assisted *T*=R.T./60 ºC *t*=0-20 min *V-ratio*(N/S)=10/90-90/10 **Uniqsis glass chip microreactor** *T*=R.T.-100 ºC *t*=2-10 min *V-ratio*(N/S)=50/50	Aromatic compounds / HNO_3-H_2SO_4	**OFAT** **(for reaction (a))** **PTFE tubular reactor** Ultrasonic assisted *T*=R.T. *t*=15 min *V-ratio*(N/S)=50/50 **(a) Yield(P1&P2)=100%** **Sel.(P1/P2)=80%/20%** **(b) Yield(P1&P2)=97%** **Sel.(P1/P2)=58%/42%** **(c) Yield(P1&P2)=97%** **Sel.(P1/P2)=64%/36%** **(d) Yield(P1&P2)=95%** **Sel.(P1/P2)=22%/78%** **Uniqsis glass chip**	Chemtrix glass chip microreactor (300 μm channel width, 120 μm channel depth)/PTFE tubular reactor(ID 0.8 mm)/Uniqsis glass chip reactor

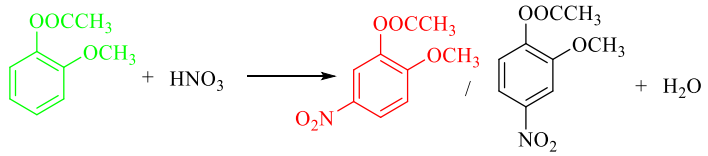
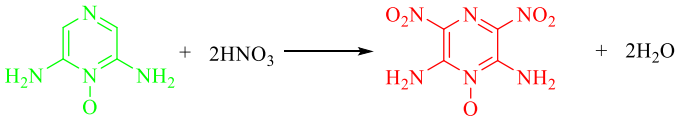
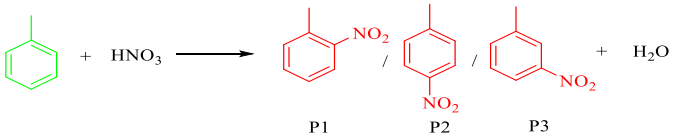
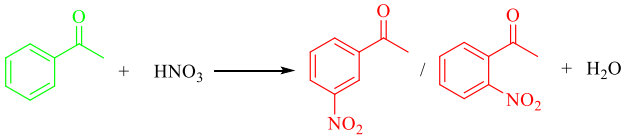
			microreactor *T*=R.T. *t*=6 min *V-ratio*(N/S)=50/50 **(a) Yield(P1&P2)=90%** **Sel.(P1/P2)=95%/5%** **(b) Yield(P1&P2)=88%** **Sel.(P1/P2)=73%/17%** **(c) Yield(P1&P2)=90%** **Sel.(P1/P2)=75%/25%** **(d) Yield(P1&P2)=90%** **Sel.(P1/P2)=7%/93%**	
Cardinal-David, B. et al (2021) [17]				
	Solvent-free N/A	Aromatic compounds / KNO_3-H_2SO_4	N/A Solvent-free **Processing amount =50kg SM/24h** **Purity=98+%** **Yield=98+%(potency-adjusted)** **Byproduct= <1%**	CSTR flow reactor
Hussain, A. et al (2021) [18] & Sharma, M. et al (2019) [19]				
	1,2-dichloroethane(DCE) *t*=7-20 min *T*=50-90 °C *M-ratio*(N/SM)=2.5-3.8 Reactant composition=60-90% Notes: Parameters were checked at the pilot scale	Aromatic compounds / HNO_3	**Kinetic Modeling** **Production rate=2 kg/h**	Pinched tubular reactor(D 1/4 inch)
Kyprianou, D. et al (2020) [20]				
	H_2SO_4 Conc.(SM in H_2SO_4)=0.56-1.1 M *T*= 110-150 °C *t*=10-30 min *M-ratio*(N/SM)=1~5	Aromatic compounds / HNO_3-H_2SO_4	**DoE** Conc.(SM in H_2SO_4)=0.56 M *T*= 130 °C *t*=20 min *M-ratio*(N/SM)=3 **Conv.=99+%**	Tubular reactor(3 mm diameter)
Chen, P. et al (2020) [21]				
	Solvent-free *T*= -30-0 °C *t*=2-19 min *M-ratio*(N/S)=0.8-9.5 *M-ratio*(N/SM)=1.4-4.8	Aromatic compounds / HNO_3-H_2SO_4	**OFAT** Solvent-free *T*= 0 °C *t*=16 min *M-ratio*(N/S)=4.6 *M-ratio*(N/SM)=3.77 **Yield=96.4%**	Stainless steel tubular reactor(ID 4 mm, OD 6.5 mm)

Köckinger, M. et al (2020) [22]	 SM1 SM2	**HAc** (a) Conc.(SM2 in reactor)=0.33/0.5 M *T*=20-80 °C *t*=0.5-16 min *M-ratio*(N/SM2)=15/30 (b)Conc.(SM in reactor)=0.364-0.459 M *T*=20/40 °C *t*=40-180 s *M-ratio*(N/SM)=4-16 (c)Conc.(SM1 in AcOH)=0.5M *T*=20°C/20-30 °C *M-ratio*(N/SM1)=1.15-3 *M-ratio*(S/SM1)=0.15-1.15	Aromatic compounds / (a) 69% HNO_3 (b) 100% HNO_3-H_2SO_4 (c) 100% HNO_3/fuming H_2SO_4	**OFAT** Solvent HAc (a)Conc.(SM2 in reactor)=0.33 M *T*=80 °C *t*=0.5 min *M-ratio*(N/SM2)=30 **Yield=99+%** **Isolated yield=86%** (b) Telescoping of the Acetylation and Nitration Conc.(SM1 in reactor)=0.364 M *T*=20 °C *t*=65 s *M-ratio*(N/SM1)=15 **Conv.(SM1)=96%** **Sel.=95%** (c) Conc.(SM1 in AcOH)=0.5M *T*=20 °C/20-30 °C *M-ratio*(N/SM1)=1.15 *M-ratio*(S/SM1)=1.15 **Isolated yield=82%** **HPLC purity=99+%** **Throughput=5.6 g/h**	Hastelloy C22 chip microreactor+PFA tubular reactor(OD 1/8 inch, ID 0.8 mm)
Hart, T. et al (2020) [23]		N/A	Aromatic compounds / (a)HNO_3-H_2SO_4 (b)Fuming HNO_3	**N/A** (a) Solvent-free Q_{SM}=0.23 mL/min Q_{NR}=0.23 mL/min *t*=5 min *T*=80 °C *P*=80 psi **Yield=87%** **Throughput=16.6 g/h** (b) Solvent-free Q_{SM}=64.6 μL/min Q_{HNO3}=85.4 μL/min *t*=10 min *T*=65 °C **Yield=96%** **Throughput=5.7 g/h**	Chip reactor (Low-iron glass plates coated in a 0.13 mm fluorinated ethylene propylene film)
Sagmeister, P. et al (2020) [24]				

	H_2SO_4 Conc.(SM)=0.5M (95%H_2SO_4) Conc.(HNO_3)=0.6M (95%H_2SO_4) *RT*=8.6-18.7 s *M-ratio*(N/SM)=0.8-2 *T*=0-35 °C	Aromatic compounds / HNO_3-H_2SO_4	**DoE** N/A	Hastelloy (C-276) chip microreactor (reactor volume for nitration 343μL)
Zhao, S. N. et al (2019) [25]				
	Solvent-free *T*=5-45 °C Q_{total}=1.5-4.5 mL/min H_2SO_4/HNO_3/H_2O=68.11/21.89/10 wt% *M-ratio*(HNO_3/SM)=1.05 Channel size=0.6/1.0 mm Ultrasound power=0/50 W Ultrasound transmission medium=water/50 vol% aq. ethylene glycol	Aromatic compounds / HNO_3-H_2SO_4	**OFAT** N/A	Ultrasonic tubular reactor(ID.0.6mm/1.0 mm)
Zharkov, M. N. et al (2019) [26]				
	1,1,1,2-tetrafluoroethane (R134a) (a) *t*=25-100 s; *T*=20 °C; *P*=10 bar Q_{SM}=0.0565-0.2262mL/min Q_{N2O5}=0.5190-2.1740mL/min Reactor volume=0.25-1 mL *M-ratio*(N_2O_5/SM)=1.0-1.5 **(b)** *t*=13/50 s, T=20 °C *P*=10 bar, Q_{SM}=0.0496mL/min Q_{N2O5}=1.151mL/min Reactor volume=0.5/2 mL *M-ratio*(N_2O_5/SM)=2.2 (c) *t*=4-50 s; *T*=20 °C; *P*=10 bar Q_{SM}=0.0260-0.0780mL/min Q_{N2O5}=1.174-3.522mL/min Reactor volume=0.25-1 mL *M-ratio*(N_2O_5/SM)=3.3-3.6	Aliphatic compounds / N_2O_5	**OFAT** Solvent R134a (a) *t*=25-100 s; *T*=20 °C; *P*=10 bar Q_{SM}=0.0565-0.2262mL/min Q_{N2O5}=0.5190-2.1740mL/min Reactor volume=0.25-1 mL *M-ratio*(N_2O_5/SM)=1.0-1.5 **Conv.=87%~100%** **(b)** *t*=13/50 s, *T*=20 °C *P*=10 bar, Q_{SM}=0.0496mL/min Q_{N2O5}=1.151mL/min Reactor volume=0.5/2 mL *M-ratio*(N_2O_5/SM)=2.2 **Conv.=90/99%** **Sel.=100%** (c) *t*=4-50 s; *T*=20 °C; *P*=10 bar Q_{SM}=0.0260-0.0780mL/min Q_{N2O5}=1.174-3.522 mL/min Reactor volume=0.25-1 mL *M-ratio*(N_2O_5/SM)=3.3-3.6 **Conv.=96~100%** **Sel.=75~96%**	Steel tubular reactor(ID 0.03 inch)

Russo, D. et al (2019) [27] Russo, D. et al (2017) [28]	 P1 P2			
	Solvent-free x_n=0.080-0.450 x_s=0.270-0.450 T=45-68 ºC C_{SM}=0.05-0.5 M Q_{MA}=0.20-9.99 mL/min Q_{SM}=1.029-103.0 μL/min V_R=1.5-4.5 mL	Aromatic compounds / HNO_3-H_2SO_4	**Kinetic modeling (for P1)** Solvent-free x_n=0.35; x_s=0.45; T=68 ºC **Yield $_{av}$(P1)=41.6%** **SPY(P1)=0.33g·L^{-1}·s^{-1}(C_{SM}=0.05M)** **SPY(P1)=3.29g·L^{-1}·s^{-1}(C_{SM}=0.5M)** **Kinetic modeling (for P2)** Solvent-free x_n=0.130; x_s=0.318; T=68 ºC C_{SM}=0.05 M **Yield $_{av}$(P2)=96%** **SPY(P2)=0.12g·L^{-1}·s^{-1}**	Commercial glass chip microreactor (Little Things Factory XXL-ST-04)
Sharma, Y. et al (2018) [29]	 P1 P2 P3			
	Solvent-free t=2.64-10 min T=0-40 ºC *M-ratio*(N/SM)=1-4	Aromatic compounds / Fuming HNO_3	**OFAT** Solvent-free t=6.4 min T=10 ºC *M-ratio*(N/SM)=4 **Yield(P1/P2/P3) =79%/20%/1%**	AMaR1 micromixer+316 SS tubular reactor (OD 1/8 inch)
Rakshit, S. et al (2018) [30]				
	Sulfolane t=3.4-11.3 min T=35-45 ºC *M-ratio*(N/SM)=8.0-8.7	Aromatic compounds / Fuming HNO_3	**OFAT** Solvent sulfolane t=8.5 min T=45 ºC *M-ratio*(N/SM)=8.7 **Yield=~70%**	Hastelloy(C22) tubular reactor(ID 1.8 mm)
Wen, Z. H. et al (2017) [31]	 P1 P2 P3 P4			
	Solvent-free *M-ratio*(N/SM)=0.85-1.00 *M-ratio*(S/N)=4 Water content φ= 88~98 wt% t=4-16 s T=273-293 K Q_{total}=1.0-3.5 mL/min(for microchannel reactor) Q_{total}=1.0-9.0 mL/min(for micro packed-bed reactor)	Aromatic compounds / HNO_3-H_2SO_4	**OFAT** Solvent-free *M-ratio*(N/SM)=1.1 *M-ratio*(S/N)=4 Water content φ=97 wt% T=273 K Q_{or}=0.4 mL/min Q_{aq}=0.9 mL/min **Conv.=99.6%** **Sel.(P1/P2/P3/P4)= 90.97%/7.26%/0.08%/ 1.04%**	Microchannel reactor (SS tubular reactor, ID 0.6 mm); micro packed - bed reactor (tubular reactor, ID 0.6 mm +packed tubular reactor, ID 6 mm(packed with quartz sand microparticles))

Cantillo, D. et al (2017) [32]				
	Solvent-free Mixing Mode = T-mixer /T-mixer(Sonicated)/ Static glass mixer (IV 1.5mL, Uniqsis) *M-ratio*(N/SM)=2.5 Conc.(HNO_3 in Oleum)= 5M *T*=60/(rt+60) °C *t*=0-31 min	Aromatic compounds / 100%HNO_3-Oleum	**OFAT** Solvent-free *M-ratio*(N/SM)=2.5 Conc.(HNO_3 in Oleum)= 5M *T*=60 °C *t*=22 min **Yield=93%** **Isolated Yield=92%**	T-mixer/T-mixer(Sonicated)/Static glass mixer(IV 1.5mL)+PFA tubular reactor(ID 0.8mm, OD1.59mm)
Li, L. et al (2017) [33] [33]				
	Solvent-free *T*=286-307 K *t*=3-10 s Water content=3%-10% *M-ratio*(N/SM)=0.7-1.6 *M-ratio*(S/N)=2	Aliphatic compounds / HNO_3-H_2SO_4	**OFAT** Solvent-free *T*=298 K *t*=10 s Water content=3% *M-ratio*(N/SM)=1.54 *M-ratio*(S/N)=2 **Conv.=99+%** **Sel.=99+%**	SS tubular reactor(ID 0.6 mm)
Chentsova, A. et al (2016) [34]				
	Dichloromethane(DCM) **SM(α-acetylbutyrolactone)** Conc.(SM)=0.36 M *M-ratio*(N/SM)=1.2-1.4 *M-ratio*(S/N)=4-10 *t*=28-54 s *T*=0-15 °C	Aliphatic compounds / HNO_3-H_2SO_4	**OFAT** Solvent DCM Conc.(SM)=0.36 M *M-ratio*(N/SM)=1.4 *M-ratio*(S/N)=7.8 *t*=54 s *T*=10 °C **Conv.=95+%** **Yield=80%** **Isolated Yield=78%**	ETFE T-mixers+PTFE tubular reactor(ID 0.76 mm, OD 1.59 mm)
Yu, Z. et al (2016) [35]				
	H_2SO_4 **Isothermal Mode** ***Mononitration*** *M-ratio*(N/SM)=1.05-1.2 *M-ratio*(S/N)=1.67-8.33 *t*=6-60 s *T*=40-100 °C Conc.(H_2SO_4)=70-98 wt% LHSV=60-600 h^{-1} ***Dinitration*** Conc.(H_2SO_4)=80 wt% *M-ratio*(N/SM2)=1.2 *M-ratio*(S/N)=6.25 LHSV=240 h^{-1} *t*=5-60 s *T*=40-120 °C **Adiabatic Mode** Conc.(H_2SO_4)=80 wt% *M-ratio*(N/SM)=1.2	Aromatic compounds / Fuming HNO_3-H_2SO_4	**OFAT** Solvent H_2SO_4 **Isothermal Mode** ***Mononitration*** Conc.(H_2SO_4)=80 wt% *t*=15 s *T*=80 °C LHSV=240 h^{-1} *M-ratio*(N/SM2)=1.2 *M-ratio*(S/N)=6.25 **Yield=98%** **Purity=99%** **Adiabatic Mode** Conc.(H_2SO_4)=80 wt% *M-ratio*(N/SM)=1.2 *M-ratio*(S/N)=2.9 *t*=5 s *T*=adiabatic **Yield=98%**	**Isothermal Mode** SS 316 T-mixer (ID, 1.5 mm)+SS316 tubular reactor (ID 3mm, OD 5mm) **Adiabatic Mode** PTFE tubular reactor(ID 3mm)

	M-ratio(S/N)=2.5-7.5 *t*=0-8 s *T*=adiabatic		**Purity=99%**	
Zhang, C.Y. et al (2016) [36]				
	HAc *t*=0-2 min *T*=100-130 °C *M-ratio*(N/SM)=1-4 Conc.(HNO_3 in Mixed)=20%-100% *P*=0.7 MPa	Aromatic compounds / Fuming HNO_3-HAc	**OFAT** Solvent HAc *t*=2 min *T*=120 °C *M-ratio*(N/SM)=2.6 Conc.(HNO_3)=40% *P*=0.7 MPa **Yield=90.7%**	Tubular reactor(ID 2 mm)
Zuckerman, N. B. et al (2015) [37]				
	Oleum *T*=10-40 °C *t*= 6-10 min t_{chip}=8-60 min *M-ratio*(NO_2^+/SM)=2.2-4.9	Aromatic compounds / 90% HNO_3-Oleum & KNO_3-Oleum	**OFAT** Solvent oleum *M-ratio*(NO_2^+/SM)=3.8 *t*=9 min **Yield=49%**	Glass chip reactor/ETFE tubular reactor/Glass bead packed column
Raimondi, N. D. M. et al (2015) [38]				
	Solvent-free Acid strength=0.75-0.80 *T*=23-35 °C *t*=40-50 s Q_{SM}=0.9-1.1 L/h Q_{MA}=1.4-1.8 L/h *M-ratio*(SM/HNO_3)=1.5	Aromatic compounds / HNO_3-H_2SO_4	**OFAT** Solvent-free Acid strength=0.80 *T*=27 °C *t*=50 s *M-ratio*(SM/HNO_3)=1.5 Conv.=33.7% Sel.=95.1% P1/P2/P3=54.8/40.5/4.6	SiC heat exchanger chip reactor (square section meandering channel, 2mm in depth)
Tibhe, J. et al (2014) [39]				
	H_2SO_4 *T*=0-25 °C *t*= 3-10 min SM/H_2SO_4(Q_{SM})=1:2.58 v/v HNO_3/H_2SO_4(Q_{MA})=1:1.5 v/v Q_{SM}/Q_{MA}=0.8~2 v/v	Aromatic compounds / HNO_3-H_2SO_4	**OFAT** Solvent H_2SO_4 *T*=10 °C *t*=10 min SM/H_2SO_4(Q_{SM})=1:2.5 w/v HNO_3/H_2SO_4(Q_{MA})=1:1.5 v/v Q_{SM}/Q_{MA}=1:1.66 v/v **Conv.=100%** **Yield=98.55%**	316L SS tubular reactor

Note: In the reaction scheme, the starting materials are marked in yellow, and the main products are labeled in red. Analysis methods follows convention: pure OFAT screening is termed OFAT; analyses incorporating DoE frameworks (even with OFAT elements) are classified as DoE.

NOMENCLATURE

A	pre-exponential factor
Ac_2O	acetic anhydride
ARC	accelerating rate calorimetry
C80	Calvet calorimeter C80
C_{NA}	the concentrations of NA
C_{NA}^0	the initial concentration of HNO_3
$C_{NO_2^+}$	the concentrations of NO_2^+
Conc.	concentration
Conv.	conversion
C_{SM}	the concentration of SM
C_{SM}^0	the initial concentrations of SM
CSTR	continuous stirred tank reactor
Da_{II}	second Damköhler number
DCM	dichloromethane
DCE	1,2-dichloroethane
DoE	design of Experiments
DSC	differential scanning calorimetry
E_a	activation energy
HAc	acetic acid
Ha	Hatta number
ΔH_D	heat of decomposition
k_2^*	the observed second-order reaction rate constant related to the NO_2^+
k_{obs}	the observed reaction rate constant based on HNO_3
LHSV	liquid hourly space velocity
M	the stoichiometric feed ratio of HNO_3 to SM
M_c function	represents the acidity of H_2SO_4
M/M	mole/mole
M-ratio (N/SM)	the molar ratio of HNO_3 to starting material
M-ratio (N/S)	the molar ratio of HNO_3 to H_2SO_4
MTSR	maximum temperature of the synthesis reaction
MTT	maximum temperature for technical reason
MW	molecule weight
n	a thermodynamic parameter that depends on the nitration substrate
NA	HNO_3
OB	oxygen balance
OFAT	one-factor-at-a-time

Q_A	the flow rate of acid
Q_{aq}	the flow rate of aqueous phase
Q_{MA}	the flow rate of mixed acid
Q_{or}	the flow rate of organic phase
Q_{SM}	the flow rate of SM
Q_{total}	total flow rate
R134a	1,1,1,2-tetrafluoroethane
RC1	reaction calorimeter
RT	residence time
R.T.	room temperature
Re	Reynolds number
Sel.	selectivity
SM	starting material
STY	space time yield
T	temperature
ΔT_{ad}	adiabatic temperature rise
T_{D24}	the initial temperature when TMR_{ad} equals 24 h
TMR_{ad}	time to maximum rate under adiabatic condition
TP	throughput
T_P	temperature of process
v/v	volume/volume
V-ratio (N/S)	the volume ratio of HNO_3/H_2SO_4
V_R	the volume of reactor
w_{AA}	the mass fraction of acetic anhydride
w/w	weight/weight
X	the conversion of SM
x_n	nitric acid molar fraction
x_s	sulfuric acid molar fraction
φ	*water content*
γ^*	the activity coefficients of the transition intermediate
$\gamma_{NO_2^+}$	the activity coefficients of NO_2^+
γ_{SM}	the activity coefficients of SM

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