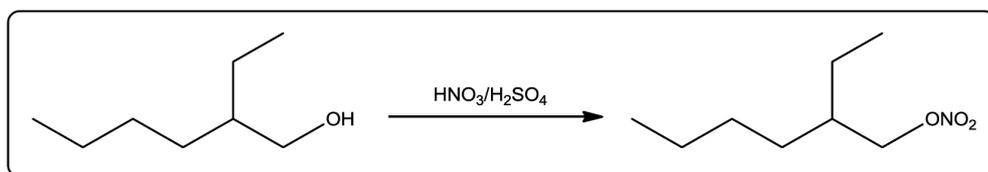


Dr Charlotte Wiles

Chemtrix BV

Solvent-free, Continuous Flow Synthesis of Nitroesters using Labtrix®-S1 Ultra Flex



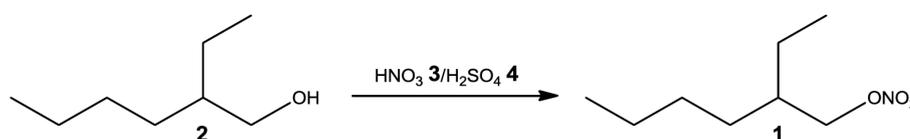
Introduction: Nitration reactions are industrially important finding application in pharmaceutical, fine chemical and agrochemical sectors, for the preparation of materials such as API's, dyes, pesticides and explosives. The fact that such reactions are rapid and exothermic, however makes their safe, controlled and selective [1] use at scale challenging. With this in mind, the past decade has seen numerous researchers demonstrating the application of continuous flow reactors to obtain control for these exothermic reactions. Pelleter and Renaud [2] from AstraZeneca demonstrated the nitration of a series of electron-rich heteroaromatic substrates at a rate of 0.8-1.1 g h⁻¹ and Brocklehurst *et al.* [3] of Novartis synthesised 8-bromo-1*H*-quinolin-2-one at 97 g h⁻¹. In addition, academic researchers have assessed the nitration of toluene [4-6] and synthesis of *o*/*m*-benzaldehyde [7].

The manipulation of highly corrosive media within flow systems is however challenging and requires careful selection of wetted materials. With this in mind, Chemtrix BV have developed Labtrix® Ultra Flex, an upgrade to the standard PEEK system, which comprises of ETFE and perfluoroelastomer wetted parts. As this upgrade can be retrofitted, it allows the chemical working range of existing Labtrix®-S1 and Start systems to be expanded (Figure 1).



Figure 1. Illustration of the (left) Labtrix® Start and (right) Labtrix®-S1 micro reactor systems from Chemtrix BV.

2-Ethyl hexyl nitrate Synthesis: 2-Ethyl hexyl nitrate **1** is an industrially important material owing to its application as a diesel additive (cetane improver) however the thermal instability of the material **1** presents a thermal hazard [8], with semi-batch processes limited to 10 °C. With this in mind, the solvent-free synthesis of 2-ethyl hexyl nitrate **1** [9] *via* the nitration of 2-ethyl-1-hexanol **2** is demonstrated using Labtrix®-S1 Ultra Flex (Scheme 1) at 0 to 40 °C (7.5 to 60 s).



Scheme 1. Model reaction used to demonstrate continuous flow nitrations using Labtrix®-S1 Ultra Flex.

Experimental Conditions: Reactions were performed using a Labtrix®-S1 (Figure 1 (right)) with an Ultra Flex upgrade (20 bar BPR) and fitted with a 3222 glass micro reactor (Volume = 5 μ l). Reagents were dosed into the reactor using 3 x 1.0 ml gas-tight syringes (SGE) and samples were automatically collected into 2 ml septum capped GC vials.

Throughout the investigation, un-diluted 2-ethyl-1-hexanol **2** was employed as feed A and the acid type and composition varied *via* feedline B so as to assess the effect on nitroester **1** formation. Prior to sample collection, DI H₂O was added through the quench inlet in order to terminate the reaction and prepare the sample for offline analysis. The reaction product (25 μ l) was collected into 50 μ l of saturated aqueous sodium hydrogen carbonate and extracted into hexane (100 μ l). Separation and analysis of the organic fraction (20 μ l) by GC-MS enabled the percentage conversion of 2-ethyl-1-hexanol **2** to 2-ethyl hexyl nitrate **1** to be determined.

NOTE: This reaction must be performed using the PEEK-free Labtrix® Ultra Flex upgrade set and is not compatible with the standard Labtrix® Start and S1 systems or the Labtrix® Flex set.

Materials: 2-Ethyl-1-hexanol **2** (>99.6 %, Sigma-Aldrich), 2-ethylhexyl nitrate **1** (97 % Sigma-Aldrich), nitric acid **3** (69-72 %, Fisher Scientific), sulfuric acid **4** (98 %, Fisher Scientific) and glacial acetic acid (99.9 %, Fisher Scientific).

Analytical Evaluation: The reaction mixture was analysed, after neutralisation with saturated sodium hydrogen carbonate (aqueous) and extraction into hexane, by GC-MS. Analyses were executed using an Agilent 6890 Series GC system fitted with a 5973 Series mass selective detector. The analytical column used was a HP-1 (12 m (length), 0.20 mm (o.d.), 0.33 μ m (film thickness)) from Agilent Technologies and the analytical method employed an injector temperature of 250 $^{\circ}$ C, an injection volume of 1.0 μ l and a split ratio of 50:1. The oven started at 50 $^{\circ}$ C (4 min hold) and ramped to 120 $^{\circ}$ C at 25 $^{\circ}$ C min⁻¹ to afford a 6.8 min program. Helium was used as the carrier gas at a flow rate of 1.0 ml min⁻¹ and a 4.0 min filament delay was employed. The retention times obtained were 4.33 min for 2-ethyl-1-hexanol **2** and 5.98 min for 2-ethyl hexyl nitrate **1** and a relative response factor (RRF) for the nitrate **1**/alcohol **2** was 1.039.

Results and Discussion: Employing the reactor manifold illustrated in Figure 2, the effect of nitrating solution (Table 1), reactor temperature (0 to 40 $^{\circ}$ C) and reaction time (7.5 to 60 s) were evaluated. With a wide range of reaction conditions reported in the literature an initial screen into the effect of acid composition was performed, Table 1 summarises the conditions assessed and the observations made.

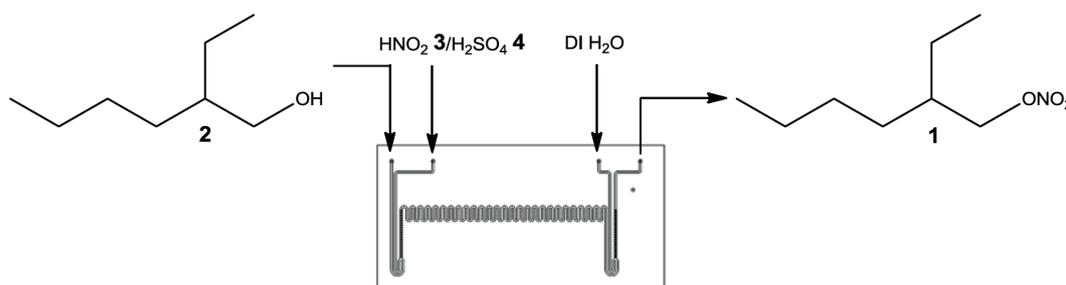


Figure 2. Reactor manifold (3222; Volume 5 μ l) used to assess the continuous flow nitration of 2-ethyl-1-hexanol **2**.

Reagent	Ratio 3:4 (eq.)	Concentration 3:4 (M)	Ratio 3:2 (eq.)	Product 1	By-product
HNO ₃ 3	1:0.00	15.90:0.00	3.10	×	×
HNO ₃ 3 :H ₂ SO ₄ 4	1:0.286	12.75:3.60	2.50	×	✓
HNO ₃ 3 :H ₂ SO ₄ 4	1:0.767	9.54:7.32	1.50	Minimal	✓
HNO ₃ 3 :H ₂ SO ₄ 4	1:1.130	7.95:9.00	1.25	✓	✓
HNO ₃ 3 :H ₂ SO ₄ 4	1:1.726	6.36:10.98	1.00	✓	×

Table 1. Effect of acid composition on the formation of 2-ethyl hexyl nitrate **1** in Labtrix®-S1 Ultra Flex.

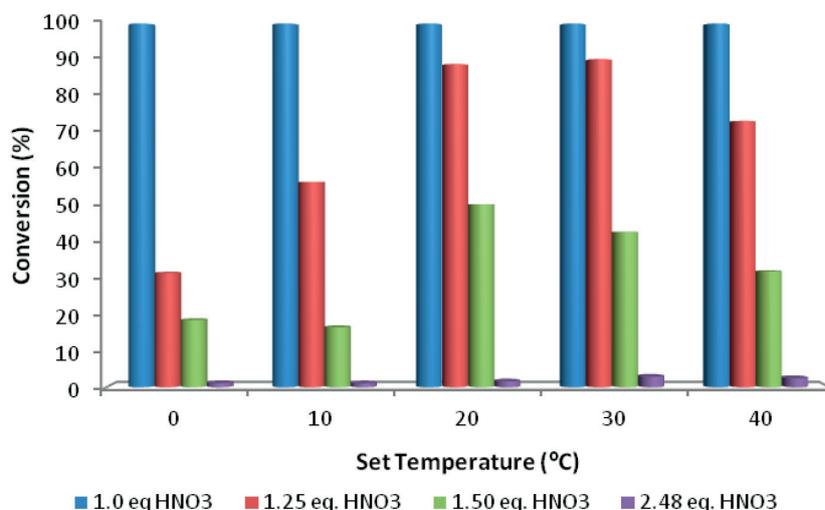


Figure 2. Graph illustrating the effect of HNO₃ **3** equivalents (eq.) on the formation of an aliphatic nitro ester **1**.

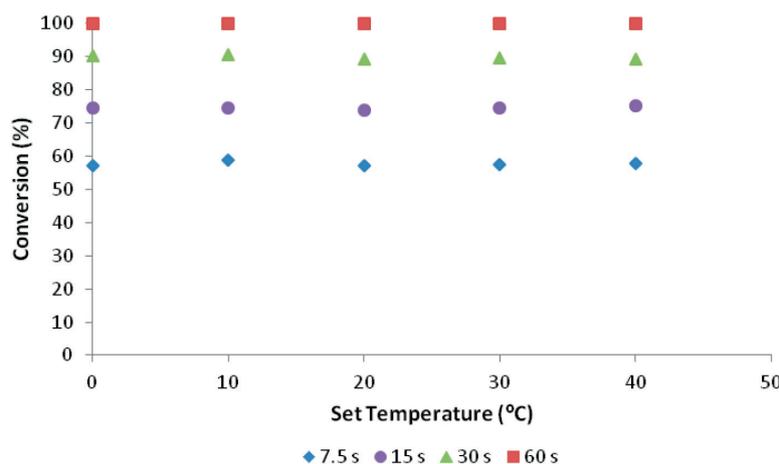


Figure 3. Graph illustrating the effect of reaction time and temperature on the conversion of 2-ethyl-1-hexanol **2** to 2-ethyl hexyl nitrate **1** in Labtrix®-S1 Ultra Flex.

Conclusion: As Table 1 illustrates, in the absence of sulfuric acid **4**, no significant nitration reaction was observed however upon addition of H₂SO₄ **4**, conversion to 2-ethyl hexyl nitrate **1** was obtained. Figure 2/3 illustrates that at temperatures of 0 to 40 °C, optimal conditions were obtained with 1.0 eq. of HNO₃ to 2-ethyl-1-hexanol **2** with no by-product formation; as observed for increased ratio's of nitric acid **3**. Investigating further the effect of reaction time and temperature, Figure 3 demonstrates that reaction temperature has little effect on the nitration of 2-ethyl-1-hexanol **2** allowing the nitration reaction to be performed at higher temperatures than safely permissible in batch (10 °C) [8].

Using the solvent-free nitration of 2-ethyl-1-hexanol **2** as a model reaction, the effect of reactor temperature (0-40 °C), reaction time (7.5 to 10 s), acid ratio (1.0 to 3.10 eq. HNO₃ **3**) and composition (HNO₃ **3** + H₂SO₄ **4**) was assessed in Labtrix®-S1 Ultra Flex. Optimal conditions were found to be a reaction time of 60 s, 1.0 eq. HNO₃ **3** and a reactor temperature of 40 °C, affording the target 2-ethyl hexyl nitrate **1** in quantitative conversion, at a throughput of 336 mg h⁻¹.

NOTE: This reaction must be performed using the PEEK-free Labtrix® Ultra Flex upgrade set and is not compatible with the standard Labtrix® Start and S1 systems or the Labtrix® Flex set.

Table 2 illustrates the various chemical working space accessible with the Labtrix® standard, Flex and Ultra Flex packages.

Reagent/Solvent	Max. Conc.	Standard (PEEK)	Flex (PPS)	Ultra Flex (ETFE)
Hydrochloric acid	36%	✗	✓	✓
Trifluoroacetic acid	99%	✗	✓	✓
Nitrobenzene	99%	✗	✓	✓
Sulfuric acid	98%	✗	✓	✓
Acetic acid	Glacial	✗	✓	✓
Butyl lithium	2.5 M	✗	✓	✓
Nitric acid	70%	✗	✗	✓
Working Range (°C)		-15 to 195	-15 to 195	-15 to 75

Table 2. Summary of the chemical compatibilities of the various Labtrix® packages (Standard = PEEK & perfluoroelastomer, Flex = PPS & perfluoroelastomer and Ultra Flex = ETFE & perfluoroelastomer).

References:

- [1]. T. G. Bonner and D. E. Frizel, *J. Chem. Soc.*, 1959, 3894-3901.
- [2]. J. Pelleter and F. Renaud, *Org. Proc. Res. Dev.*, 2009, **13**, 698-705.
- [3]. C. E. Brocklehurst, H. Lehmann and L. La Vecchia, *Org. Proc. Res. Dev.*, 2011, **15**, 1447-1453.
- [4]. J. R. Burns and C. Ramshaw, *Chem. En. Commun.*, 2002, **189**, 1611-1628.
- [5]. Y. Su, Y. Zhao, F. Jiao, G. Chen and Q. Yuan, *AIChE J.*, 2011, **57**(6), 1409-1418.
- [6]. R. Halder, A. Lawal and R. Damavarapu, *Catal. Today*, 2007, **125**, 74-80.
- [7]. A. A. Kulkarni, V. S. Kalyani, R. A. Joshi and R. R. Joshi, *Org. Proc. Res. Dev.*, 2009, **13**, 999-1002.
- [8]. L. Chen, T. Liu, Q. Yang and W. Chen, *J. Loss Prevent. Proc. Ind.*, 2012, **25**(3), 631-635.
- [9]. J. Shen, Y. Zhao, G. Chen and Q. Yuan, *Chin. J. Chem. Eng.*, 2009, **17**(3), 412-418.