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Scalable Flow Chemistry

Application Note 2

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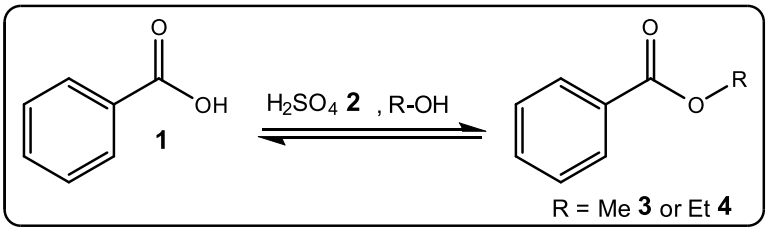
Application Note 2: Continuous Flow Esterifications using Mineral Acid Catalysis



Esters are widely employed within the chemical industry, with many low molecular weight derivatives finding application in flavours and fragrances and tert-butyl esters finding application as protecting groups. The reversible nature of the reaction can however prove problematic, especially when reactions are performed on an industrial-scale. In this application note, we report the performance of two esterification reactions utilizing benzoic acid **1** as the substrate in each case and the mineral acid sulfuric acid **2**, as a means of demonstrating the high ester conversions attainable within short reaction times.

Reaction Conditions: Reactions were performed using a Labtrix® S1 system (Figure 1a), fitted with a glass micro reactor (Reactor volume = 10 µl (3023)) and 2 x 1000 µl gas-tight syringes (SGE). A 25 bar ULDV-BPR (Upchurch Scientific) was fitted to the system and used for all experiments in order to maintain reactants in the liquid phase. Two stock solutions (5 ml) were prepared and comprised of benzoic acid **1** (0.1 M) and sulfuric acid **2** (0.11 M) in the alcohol under investigation.

Prior to performing a micro reaction, the micro reactor was filled with the desired alcohol at a total flow rate of 25 µl min^{-1} for 5 min, after which time the syringes were replaced with those containing the aforementioned stock solutions and the reactor primed, again at a total flow rate of 25 µl min^{-1}, for 20 min (25 °C). Reaction mixtures were collected over a period of 5-10 min at preset intervals and analysed offline using HPLC-UV (Column = Luna C18 (Phenomenex), Mobile phase = 80:20 H_2O:MeOH, Flow rate = 1.0 ml min^{-1} at 254 nm) with retention times compared to fully characterized synthetic standards.

(a).

(b).

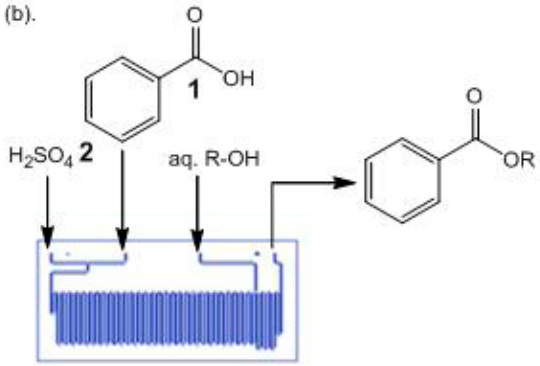


Figure 1. Illustration of (a). Labtrix® S1 the micro reactor development equipment used in this investigation and (b). a schematic of micro reactor (3023) set-up employed.

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Reaction Optimisation: Employing total reactant flow rates ranging from 1.0 to 20.0 µl min^{-1} (Residence times = 10 to 0.5 min) the effect of reactor temperature (25 to 175 °C) was investigated on the synthesis of methyl benzoate **3** (Figure 2), using MeOH, and ethyl benzoate **4** using EtOH (Table 1). In all cases, reaction conditions were evaluated three times to ensure a stable and reproducible reaction system was developed, with errors (% RSD) observed to range between 0.09 and 0.68 %.

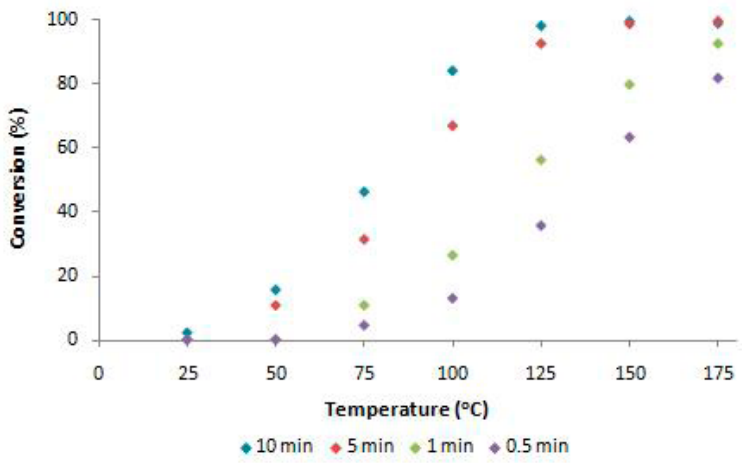


Figure 2. Summary of the results obtained for the continuous flow synthesis of methyl benzoate **3**.

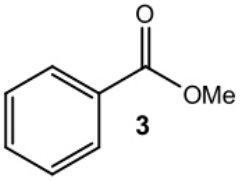
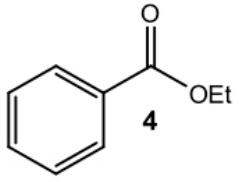
		Temperature (°C)						
Product	Time (min)	25	50	75	100	125	150	175
 **3**	0.5	0	0	4.50	12.94	35.69	63.34	81.83
	1.0	0	0	10.77	26.39	56.23	79.81	92.62
	5.0	0	10.73	31.35	66.85	92.58	98.71	99.59
	10.0	2.56	16.02	46.60	84.50	98.49	100.0	99.22
 **4**	0.5	0	0	0	3.88	11.47	21.82	35.29
	1.0	0	0	0	6.85	19.02	35.50	53.26
	5.0	0	0	8.28	26.54	55.88	77.75	90.50
	10.0	0	0	16.20	37.95	73.21	90.94	94.93

Table 1. Summary of the conversions obtained for the continuous flow synthesis of methyl benzoate **3** and ethyl benzoate **4** using a Labtrix® S1 system.

Summary: As Table 1 illustrates, in order to perform mineral acid catalysed esterifications under continuous flow conditions, it is necessary to heat the reactor as no product was observed at room temperature. Conversion was observed to increase with increasing reactor temperature, enabling the identification of a residence time of 5 min and reactor temperature of 150 °C as being optimal for the synthesis of methyl benzoate **3** compared with a residence time of 10 min and a reactor temperature of 175 °C for the synthesis of ethyl benzoate **4**. Using this approach, a detailed continuous flow investigation was performed using < 46 mg of precursor **1** enabling the rapid identification of optimal processing conditions for acid catalysed esterifications.