CHEMTRIX
Scalable Flow Chemistry

Application Note 22

Dr Charlotte Wiles — Chemtrix BV

'Optimisation and Scaling of an Efficient, Catalyst-free Condensation of Acid Chlorides and Alcohols using Continuous Flow'

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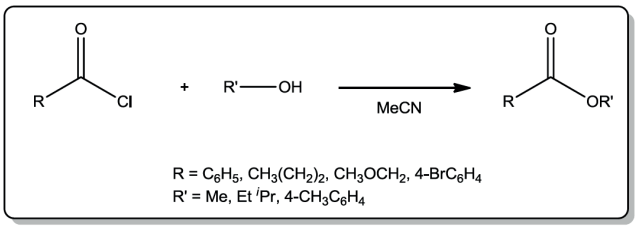


Introduction: Esters are a synthetically important class of compound that find widespread application in the fine chemical industry as flavours and fragrances and afford protection of the carboxylic acid moiety within the pharmaceutical industry [1]. Whilst esterification reactions have been widely reported under continuous flow conditions using activated esters [2], acid [3,4], base [5,6] or biocatalysts [7], or the use of super-heated alcohols [8], there have been no reports of the use of acid chlorides. Typically performed in the presence of a catalyst, the reaction of an acid chloride with an alcohol is a well-known strategy for the protection of hydroxyl functionalities, catalysts include small organic bases [9] such as pyridine, triethylamine, 4-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO) and inorganic catalysts such as $LiClO_4$, $BiCl_3$ or TiO_2 [10]. With a view to developing more sustainable, industrially relevant production methods, Stevens and co-workers [11] investigated the ability to perform the reaction of acid chlorides and alcohols in the absence of a catalyst and, where reagents permitted, in the absence of a reaction solvent. In addition to reducing processing costs, removal of the catalyst also has the added advantage that product isolation is simplified – with only alcohol removal required after reaction.

Catalyst-free Esterification under Flow Conditions: In order to develop an efficient, catalyst-free esterification method, Stevens and co-workers utilised Labtrix® Start (Figure 1), a manually operated micro reactor development apparatus suitable for reaction optimisation at the mg-scale. Employing a glass micro reactor with a T-mixer (Device 3023; Volume = 10 µl) and 10 bar BPR, the authors investigated the solvent-free reaction of benzoyl chloride **1** with methanol, ethanol and isopropanol in order to identify the optimal alcohol stoichiometry, reaction temperature and reaction time (Figure 2) for the formation of methyl benzoate **2**, ethyl benzoate **3** and isopropyl benzoate **4** respectively. Using offline GC-FID and IR analysis, the authors quantified the proportion of ester formed and the results obtained can be found summarised in Table 1.

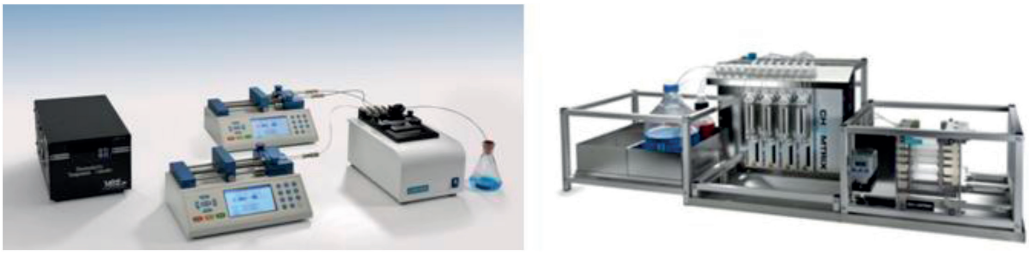


Figure 1. Photographs illustrating the turn-key scalable flow chemistry platform from Chemtrix BV; (left) Labtrix® Start and (right) KiloFlow®.

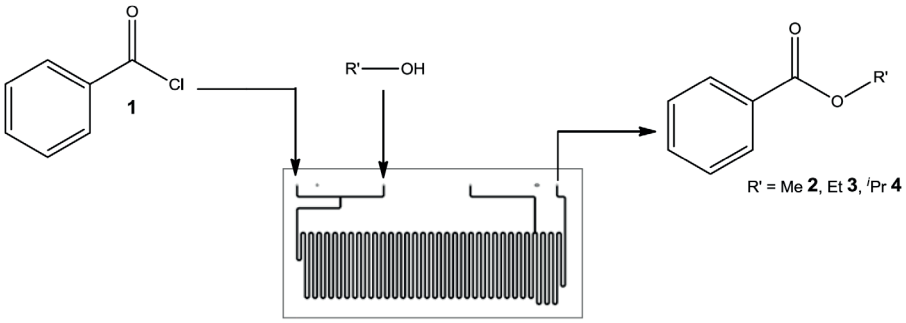


Figure 2. Schematic illustrating the reaction manifold used to assess the esterification of benzoyl chloride **1** under catalyst-free, continuous flow conditions.

Alcohol	Temperature (°C)	Residence Time (s)	Alcohol (Equiv.) 1.0	1.1	1.2	1.3	1.5	2.0
MeOH	80	100	-	-	-	-	-	97
	80	200	-	-	96	-	98	97
	80	300	95	-	99	100	-	-
	90	300	95	-	-	-	-	-
	100	300	-	99	-	-	-	-
EtOH	80	300	-	-	-	88	93	98
	100	300	-	-	-	99	-	-
	110	300	-	95		100	-	-
	130	300	-	99	-	-	-	-
	130	400	-	99	-	-	-	-
	140	300	-	99	-	-	-	-
	140	400	-	99	-	-	-	-
iPrOH	80	300	-	-	-	-	-	61
	100	300	-	-	-	92	95	-
	110	300	-	-	-	99	100	-
	120	300	-	-	-	100	-	-

Table 1. Summary of the results obtained for the reaction of benzoyl chloride **1** with MeOH, EtOH and iPrOH within Labtrix® Start.

Long-term Reactor Performance: Having identified the optimal conditions for the formation of a series of benzoate derivatives, the Labtrix® micro reactor was operated for 5.6 h at 300 s in order to evaluate the isolated yield of the methylation reaction. As a catalyst-free system was employed, product isolation was achieved by simply concentrating the product *in vacuo*, to remove any excess MeOH, which afforded the target methyl benzoate **2** as a colourless oil in 90 % yield.

Scope of the Catalyst-free Method: In an extension to the investigation, a series of acid chlorides were assessed and in the case of solid substrates, a reaction solvent was employed (DCM, dioxane or MeCN) to prevent fouling of the micro channels. The optimal conditions for each substrate/alcohol reaction can be found summarised in Table 2.

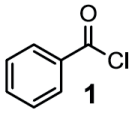
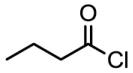
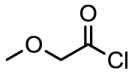
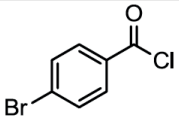
Acid Chloride	Alcohol	Residence Time (s)	Temperature (°C)	Alcohol (Equiv.)	Conversion (%)
 **1**	MeOH	300	80	1.3	100
	EtOH	300	110	1.3	100
	^{i}PrOH	300	120	1.3	100
	p-Cresol (2 M)	400	140	2	98
	MeOH	300	80	1.3	100
	EtOH	300	110	1.3	100
	^{i}PrOH	300	120	1.3	100
	p-Cresol (2 M)	400	140	2	99
	MeOH	300	80	1.3	91
	EtOH	300	110	1.3	97
	^{i}PrOH	300	120	1.3	100
	MeOH	300	80	2	10
	p-Cresol (1.5 M)	400	140	2	79

Table 2. Summary of the results obtained using a range of aliphatic and aromatic acyl chlorides within Labtrix® Start.

Scaling to KiloFlow®: Having demonstrated the generality of the catalyst-free protocol towards a series of aliphatic and aromatic acyl chlorides, the authors subsequently investigated the scalability of the method; translating from a 10 µl Labtrix® reactor to a 13.8 ml KiloFlow® reactor. Employing the production of methyl benzoate **2** as a model reaction, after reaching steady state, the reaction products generated in KiloFlow® were collected over a period of 4 h, with the HCl generated during the reaction collected by bubbling dry N_2 through the reaction product and subsequently trapping it in water. Upon degassing, the reaction product was concentrated *in vacuo* to remove the excess MeOH and the title compound **2** isolated at a throughput of 2.2 g min^{-1}. Over the 4 h period, a total of 528 g (98 % yield) methyl benzoate **2** was produced and all spectra recorded were consistent with the literature.

Conclusion: The developed catalyst-free continuous flow methodology provides a green alternative to existing methods of ester synthesis and demonstrates suitable substrate generality for the preparation of aliphatic and aromatic esters. In the case of liquid reagents, the methodology allows for solvent-free processing affording the corresponding esters in high yields and purities with reaction times ranging from 5 to 7 min. When utilising solid precursors, it was found necessary to add a solvent in order to prevent fouling of the micro channels – suitable solvents were found to be DCM, dioxane or MeCN. Performing initial condition screening within Labtrix® (Reaction Volume = 10 µl) followed by 1380x up-scaling to KiloFlow®, enabled the authors to rapidly transfer the developed protocol from research to production, accessing throughputs of 2.2 g min^{-1} in a standard laboratory fume hood.

This material is taken from 'Efficient and Catalyst-free Condensation of Acid Chlorides and Alcohols using Continuous Flow', accepted for publication in the peer-reviewed Royal Society of Chemistry journal *Green Chemistry*. Please refer to the original article for a more detailed discussion [11].

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