Green Chemistry

Cite this: *Green Chem.*, 2012, **14**, 2776

www.rsc.org/greenchem

PAPER

Efficient and catalyst-free condensation of acid chlorides and alcohols using continuous flow

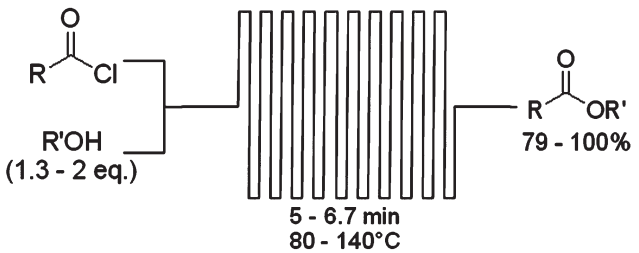
Frederik E. A. Van Waes,[a] J. Drabowicz,[b] A. Cukalovic[a] and Christian V. Stevens*[a]

Received 13th April 2012, Accepted 7th August 2012
DOI: 10.1039/c2gc35555h

An efficient, catalyst-free continuous flow procedure for the condensation of acid chlorides and alcohols was developed. Different esters could be obtained using this protocol with excellent conversions starting from the corresponding acid chlorides and alcohols in very short reaction times (5–7 min). The reaction was performed solventless for liquid reagents but requires a solvent for solid reagents in order to prevent clogging of the microreactor. Since no catalyst is needed, the purification of the reaction mixture is very straightforward. Scale-up of the reaction to a microreactor with an internal volume of 13.8 ml makes it possible to produce 2.2 g min^{-1} of ester with an isolated yield of 98% and recuperation of the formed HCl.

Introduction

The reaction between an acid chloride and an alcohol is a well-known reaction and is used extensively in organic chemistry, for example as a protection strategy for hydroxyl groups.[1] Typically, this reaction is performed in the presence of a catalyst. Among the base catalysts used for this reaction of acid chlorides, the most common are pyridine, Et_3N and 4-dimethylaminopyridine (DMAP).[1,2a] Other bases, such as 1,4-diazabicyclo[2.2.2]-octane (DABCO),[2a,b] *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)[2c] or NaOH,[2d] can also be used. Besides these bases, other catalysts are reported in the literature: $LiClO_4$,[3a] Al_2O_3,[3b–d] TiO_2,[3e] ZnO,[3f–h] $ZrOCl_2{\cdot}8H_2O$,[3i] $CeCl_3$,[3j] Tl,[3k] $BiCl_3$ [3l] and $BiFeO_3$.[3m] However, in view of an increased sustainability there is a continuous search for more straightforward processes and process intensification. In the framework of our research to use microreactor technology to develop reactions which really benefit from continuous processing, we studied the condensation of acid chlorides with alcohols.[4] Most of the catalysts mentioned above can be used solventless. Strazzolini *et al.* reported a catalyst-free reaction between acid halides and alcohols in CH_2Cl_2.[5a] However, they describe a competition between alkyl halide and ester formation. Ranu *et al.* reported a solvent-free and catalyst-free procedure for the condensation of acid chlorides and alcohols.[5b] Different alcohols were reacted with acetyl or propanoyl chloride giving the corresponding esters with an isolated yield between 88% and 93%. However, the scale of their reactions was limited to 5 mmol and the number of acid chlorides investigated was limited. For example, no aromatic acid chlorides were included. Moreover, they used as much as 20% excess of acid chloride and most of their research focussed on the use of acid anhydrides which makes the method less atom efficient in comparison to the use of acid chlorides. This prompted us to evaluate the catalyst-free condensation of acid chlorides and alcohols using continuous flow in order to develop an industrially relevant, practical, efficient, fast and green procedure (Scheme 1).



Scheme 1 Catalyst-free condensation of acid chlorides and alcohols using continuous flow.

Performing the condensation of acid chlorides and alcohols under catalyst-free conditions has also an important economical advantage because the costs for the catalyst are eliminated and the purification becomes almost redundant. Moreover, the use of microreactor technology is inherently safer than batch technology because of the small internal volume and excellent heat transfer associated with the microreactor chip. The excellent heat transfer also allows rapid heating or cooling of the reaction mixture. Although there are a few examples of the formation of esters using microreactor technology, to the best of our knowledge, this is the first procedure reported starting from acid chlorides using a catalyst-free procedure. Known esterification

[a]*SynBioC Research Group, Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Gent, Belgium. E-mail: chris.stevens@ugent.be; Fax: +32 9 264 62 21; Tel: +32 9 264 59 57*
[b]*Center of Molecular and Macromolecular Studies, Department of Heteroatom Chemistry, Polish Academy of Science, Sienkiewicza 112, 90-363 Lødz, Poland. E-mail: draj@bilbo.cbmm.lodz.pl; Fax: +48 42684; Tel: +48 42680 3234*

reactions in the literature using continuous flow include Fischer-type esterifications,[6a–c] the use of lipases[6d–f] and other types of esterification reactions.[6g–i]

Results and discussion

In preliminary batch experiments, the condensation of equimolar amounts of benzoyl chloride with ethanol was carried out at room temperature in diethyl ether. Only a trace of ethyl benzoate was detected after 21 h. However, this benzoate was isolated in quantitative yield when benzoyl chloride was reacted with a 10 molar excess of ethanol for 200 min. A similar condensation of benzoyl chloride with a 10 molar excess of methanol gave quantitatively methyl benzoate after 15 min.

To evaluate the condensation of acid chlorides and alcohols under continuous flow, the reaction between benzoyl chloride and methanol was chosen as the generic reaction. All reactions were performed solventless (unless the starting material was a solid) in a microreactor with an internal volume of 10 µl (Labrix® Start microreactor from Chemtrix).

In a first series of experiments, the optimal conditions for the microreactor procedure were developed. The reaction temperature, the residence time and the stoichiometric ratio of both reagents were varied and the results were evaluated using IR ($\nu_{C=O\ \text{benzoyl chloride}}$ = 1770 cm^{-1}; $\nu_{C=O\ \text{methyl benzoate}}$ = 1720 cm^{-1}). From these experiments, it was clear that the reaction temperature is preferable above the atmospheric boiling point of methanol (T_b = 65 °C). Good conversions were obtained with a reaction temperature of 80 °C whereas the conversion was limited at 50 °C. In order to prevent the formation of gas bubbles in the microreactor chip (HCl is formed during the reaction and the reaction mixture is heated above the atmospheric boiling point of the alcohol), a back pressure regulator (BPR) of 10 bar was used. The most important experiments were then reconfirmed in order to determine the conversion by GC (Table 1).

Full conversion of benzoyl chloride with methanol into methyl benzoate was obtained with a residence time of 300 s, a reaction temperature of 80 °C and as little as 1.3 equiv. of MeOH. In order to determine the isolated yield, the microreactor was run for 5.6 h. The work-up of the reaction mixture was very straightforward: pure methyl benzoate was obtained with a yield of 90% after evaporation of the excess MeOH. At lower residence times, traces of benzoyl chloride were detected in the reaction mixture, even if the ratio MeOH/BnCl was increased. In attempts to achieve full conversion with a stoichiometric ratio beneath 1.3, the reaction temperature was increased but without success. However, 99% conversion was obtained with a reaction temperature of 100 °C and 1.1 equiv. of MeOH.

In a next series of experiments, the optimised conditions for the condensation of benzoyl chloride and methanol were used for the condensation of benzoyl chloride and ethanol. However at a temperature of 80 °C, the stoichiometric ratio EtOH/BnCl had to be above 1.3 in order to obtain good conversions. Probably, this is due to the fact that a reaction temperature of 80 °C is close to the atmospheric boiling point of EtOH (T_b = 78 °C). Increasing the reaction temperature to 110 °C led to full conversion with 1.3 equiv. of EtOH. Excellent conversions (99%) were obtained for a stoichiometric ratio EtOH/BnCl of 1.1 when the reaction temperature was raised (130 °C or 140 °C).

Table 1 Condensation of benzoyl chloride with MeOH, EtOH or iPrOH: GC-conversion (%)

		Alcohol (equiv.)					
T (°C)	RT[a] (s)	1	1.1	1.2	1.3	1.5	2
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	—	—

[a] RT = residence time.

When benzoyl chloride was reacted with iPrOH instead of EtOH, the conversion was poor at a reaction temperature of 80 °C, even with 2 equiv. of iPrOH. Raising the reaction temperature allowed again good conversions. For the condensation of benzoyl chloride and iPrOH, the optimised conditions were a reaction temperature of 120 °C, a residence time of 300 s and 1.3 equiv. of iPrOH.

Using the optimised conditions for the different alcohols, other acid chlorides were converted into their corresponding esters (Table 2).

To extend the scope of the reaction, the continuous flow procedure was evaluated for solid acid chlorides and alcohols in solution.

In a first attempt, a solution of a solid acid chloride (4-bromobenzoyl chloride) was reacted with neat MeOH. Different concentrations of the acid chloride in different solvents (dioxane, CH_2Cl_2 or CH_3CN) were evaluated. These experiments were conducted at a reaction temperature of 80 °C and a residence time of 300 s. In the first trials, high concentrations of 4-bromobenzoyl chloride were used in order to establish a good ratio between the flows of both reagents. However, using CH_2Cl_2 (5 M) or dioxane (4 M) resulted in clogging of the microreactor channels (width = 300 µm, depth = 60 µm). Lowering the concentration to 3.25 M in dioxane or CH_3CN resulted in less than 5% conversion (GC), even if up to 3 equiv. of MeOH were used. Subsequently, the concentration of the CH_3CN-solution was lowered to 0.5 M in order to overcome possible mixing problems due to the viscosity of the 4-bromobenzoyl chloride solution. However, the conversion of the acid chloride was limited to 10% (GC).

Subsequently, a solid alcohol (*p*-cresol) in solution was reacted with neat benzoyl chloride (Table 2, entry 11). The alcohol was dissolved in dioxane or CH_3CN with a concentration

Table 2 Condensation of acid chlorides with alcohols under catalyst-free continuous flow conditions

Entry	Acid chloride[a] (M)	Alcohol[a] (M)	RT[b] (s)	T[b] (°C)	Alcohol (equiv.)	Conversion (%)
1	C_6H_5COCl	MeOH	300	80	1.3	100[c]
2	C_6H_5COCl	EtOH	300	110	1.3	100
3	C_6H_5COCl	iPrOH	300	120	1.3	100
4	$CH_3(CH_2)_2COCl$	MeOH	300	80	1.3	100
5	$CH_3(CH_2)_2COCl$	EtOH	300	110	1.3	100
6	$CH_3(CH_2)_2COCl$	iPrOH	300	120	1.3	100
7	CH_3OCH_2COCl	MeOH	300	80	1.3	91
8	CH_3OCH_2COCl	EtOH	300	110	1.3	97
9	CH_3OCH_2COCl	iPrOH	300	120	1.3	100
10	4-BrC_6H_4COCl (0.5 M)	MeOH	300	80	2	10
11	C_6H_5COCl	*p*-Cresol (2 M)	400	140	2	98
12	$CH_3(CH_2)_2COCl$	*p*-Cresol (2 M)	400	140	2	99
13	4-BrC_6H_4COCl (1.5 M)	*p*-Cresol (1.5 M)	400	140	2	79

[a] When the starting material was solid, the compound was dissolved in CH_3CN. [b] RT = residence time, T = temperature. [c] Isolated yield after running the microreactor for 5.6 h: 90%.

of 2 M. Initial experiments were conducted at a reaction temperature of 80 °C, a residence time of 300 s and 1.3 equiv. of *p*-cresol in CH_3CN. However, these conditions resulted in a limited conversion of only 25% (GC). The conversion increased (78% (GC)) by raising the temperature to 120 °C. A further increase of the reaction temperature (140 °C) in combination with a residence time of 400 s and 2 equiv. of *p*-cresol led to a conversion of 98% (GC). When these reactions were performed in dioxane, lower conversions were obtained. The optimised conditions were also applied on the condensation of butyryl chloride with *p*-cresol (Table 2, entry 12).

At last, the condensation of a solid acid chloride (4-BrC_6H_4COCl) with a solid alcohol (*p*-cresol) was evaluated when both reagents were dissolved in CH_3CN. The reactions were performed at a temperature of 140 °C and a residence time of 400 s. Initial experiments revealed that 2 equiv. of *p*-cresol are needed in order to obtain reasonable conversions. Varying the concentration of both solutions finally led to the optimal conditions in which both reagents were dissolved in CH_3CN with a concentration of 1.5 M. A conversion of 79% (GC) could be obtained (Table 2, entry 13).

In order to investigate the applicability of this reaction on an industrial scale, the developed mmol procedure was scaled–up. The optimised conditions for the condensation of benzoyl chloride and MeOH were tested with a microreactor with an internal volume of 13.8 ml (KiloFlow® microreactor from Chemtrix). The use of this system led to a capacity of 2.2 g min^{-1} methyl benzoate with an isolated yield of 98%. Moreover, the formed HCl could be recuperated by purging the reaction mixture with dry nitrogen gas and subsequently trapping the HCl vapour in water. The work-up of the reaction mixture was very straightforward. Pure methyl benzoate was obtained after evaporation of the excess MeOH. At last, the condensation of benzoyl chloride and MeOH was run for several hours on the KiloFlow® microreactor in order to monitor the conversion and yield during the course of the operation (Table 3). After reaching the steady state, the experiment was run for 4 h and samples were collected at different times. Initially, a yield of 90% was obtained which is lower than the yield of 98% in the previous experiment. After 1 h, a drop in the yield was observed after which the yield stabilised on 86–87%.

Table 3 Conversion and yield for the condensation of benzoyl chloride and MeOH during the course of the operation (KiloFlow® microreactor)

Time	Conversion[a] (%)	Yield (%)
t_0 = 0 h	92	90
t_1 = 1 h	80	80
t_2 = 3 h	87	86
t_3 = 4 h	88	87

[a] GC-conversion.

Conclusions

The developed catalyst-free continuous flow procedure provides a green alternative for the existing methods of esterification of acid chlorides. Both aliphatic and phenolic hydroxyl groups reacted with different acid chlorides with formation of the corresponding esters in excellent conversions and very short reaction times (5–7 min). The reaction was performed solventless for liquid reagents but requires a solvent for solid reagents in order to prevent clogging of the microreactor channels. Upscaling the reaction resulted in a productivity of 2.2 g min^{-1} of ester with an isolated yield of 98% and recuperation of the formed HCl which makes this reaction industrially relevant.

Experimental

All alcohols and acid chlorides are commercially available. Liquid reagents were used in neat form and, if necessary, distilled prior to use. Solid reagents were dissolved in dioxane, CH_2Cl_2 or CH_3CN.

The small-scale reactions were performed using a Labtrix® Start system (Chemtrix) (Table 4) fitted with a glass microreactor chip of 10 µl internal volume and 2 × 1000 µl gas-tight syringes (SGE). A back pressure regulator (BPR) of 10 bar was used in order to keep all reagents in solution at elevated temperatures. Before performing the reaction, the microreactor was rinsed with the alcohol or solvent under investigation. Subsequently, the microreactor was primed with the required alcohol and acid chloride using a total flow rate of 15–20 µl min^{-1} for 5–6 min.

Table 4 Technical specifications of the used microreactors

	Labtrix® Start	KiloFlow®
Channel dimensions	300 μm × 60 μm	1.4 mm × 1 mm
Wetted materials	Glass, PEEK, PTFE, Techtron	Glass, PEEK, PFA, PPS, perfluoroelastomer
Type of mixer	T-mixer	SOR mixer[a]

[a] SOR = staggered oriented ridges.

Finally, both reagents were pumped through the microreactor with a flow rate corresponding to the desired stoichiometric ratio and residence time. After a steady state period (50–65 min depending on the total flow rate, total volume of 100 μl), a sample was collected to be analyzed by GC. The formed esters are well known compounds and their spectral data correspond to the data reported in the literature.

The upscaling of the condensation of benzoyl chloride with methanol was performed using a KiloFlow® system (Chemtrix) (Table 4) with an internal reactor volume of 13.8 ml. Both benzoyl chloride and methanol were sonicated for 15 min before use. A BPR of 13 bar was used in order to keep all reagents in the liquid phase. After rinsing the microreactor with methanol, the reactor was primed with benzoyl chloride and methanol. Subsequently, both reagents were pumped through the microreactor with a total flow rate of 2.8 ml min^{-1} (F_{MeOH} = 0.9 ml min^{-1}, $F_{benzoyl\ chloride}$ = 1.9 ml min^{-1}) and thus a residence time of 5 min and a ratio MeOH/BnCl of 1.36. After reaching steady state (30 min), a sample was collected and analyzed by GC. Formed HCl was recuperated by bubbling dry nitrogen through the reaction mixture and subsequently trapping the HCl in water. After evaporating the excess of methanol, methyl benzoate was obtained with an isolated yield of 98%. Spectral data are in comparison with the literature.

Acknowledgements

Financial support for this research from the Fund for Scientific Research Flanders (FWO Vlaanderen) and the Long Term Structural Methusalem Funding by the Flemish Government is gratefully acknowledged.

Notes and references

1 W. T. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 4th edn, 2007, p. 222.
2 (*a*) K. Ishihara, H. Kurihara and H. Yamamoto, *J. Org. Chem.*, 1993, **58**, 3791; (*b*) A. R. Hajipour and G. Mazloumi, *Synth. Commun.*, 2002, **32**, 23; (*c*) T. Sano, K. Ohashi and T. Oriyama, *Synthesis*, 1999, **7**, 1141; (*d*) O. I. Volker, *Tetrahedron Lett.*, 1979, **26**, 2431.
3 (*a*) B. P. Bandgar, V. T. Kamble, V. S. Sadavarte and L. S. Uppalla, *Synlett*, 2002, **5**, 735; (*b*) V. K. Yadav, K. G. Babu and M. Mittal, *Tetrahedron*, 2001, **57**, 7047; (*c*) S. Paul, P. Nanda and R. Gupta, *Molecules*, 2003, **8**, 374; (*d*) V. K. Yadav and K. G. Babu, *J. Org. Chem.*, 2004, **69**, 577; (*e*) M. A. Pasha and K. Manjula, *Indian J. Chem.*, 2008, **47b**, 597; (*f*) F. Tamaddon, M. A. Amrollahi and L. Sharafat, *Tetrahedron Lett.*, 2005, **46**, 7841; (*g*) M. H. Sarvari and H. Sharghi, *Tetrahedron*, 2005, **61**, 10903; (*h*) R. Tayebee, F. Cheravi, M. Mirzaee and M. M. Amini, *Chin. J. Chem.*, 2010, **28**, 1247; (*i*) R. Ghosh, S. Maiti and A. Chakraborty, *Tetrahedron Lett.*, 2005, **46**, 147; (*j*) E. Torregiani, G. Seu, A. Minassi and G. Appendino, *Tetrahedron Lett.*, 2005, **46**, 2193; (*k*) E. C. Taylor, G. W. McLay and A. McKillop, *J. Am. Chem. Soc.*, 1968, **90**, 2422; (*l*) R. Ghosh, S. Maiti and A. Chakraborty, *Tetrahedron Lett.*, 2004, **45**, 6775; (*m*) S. Farhadi and M. Zaidi, *J. Mol. Catal. A: Chem.*, 2009, **299**, 18.
4 (*a*) D. R. J. Acke, R. V. A. Orru and C. V. Stevens, *QSAR Comb. Sci.*, 2006, **25**, 474; (*b*) D. R. J. Acke and C. V. Stevens, *Green Chem.*, 2007, **9**, 386; (*c*) D. R. J. Acke, C. V. Stevens and B. I. Roman, *Org. Process Res. Dev.*, 2008, **12**, 921; (*d*) T. S. A. Heugebaert, B. I. Roman, A. De Blieck and C. V. Stevens, *Tetrahedron Lett.*, 2010, **51**, 4189; (*e*) J. C. M. Monbaliu, M. Winter, B. Chevalier, F. Schmidt, Y. Jiang, R. Hoogendoorn, M. A. Kousemaker and C. V. Stevens, *Bioresour. Technol.*, 2011, **102**, 9304.
5 (*a*) P. Strazzolini, A. G. Giumanini and G. Verardo, *Tetrahedron*, 1994, **50**, 217; (*b*) B. C. Ranu, S. S. Dey and A. Hajra, *Green Chem.*, 2003, **5**, 44.
6 (*a*) A. A. Kulkarni, K. P. Zeyer, T. Jacobs and A. Kienle, *Ind. Eng. Chem. Res.*, 2007, **46**, 5271; (*b*) X. J. Yao, J. F. Yao, L. X. Zhang and N. P. Xu, *Catal. Lett.*, 2009, **132**, 147; (*c*) R. Becker, K. Koch, P. J. Nieuwland and F. P. J. T. Rutjes, *Chim. Oggi*, 2011, **29**, 47; (*d*) J. W. Swarts, P. Vossenberg, M. H. Meerman, A. E. M. Janssen and R. M. Boom, *Biotechnol. Bioeng.*, 2008, **99**, 855; (*e*) A. Pohar, I. Plazl and P. Znidarsic-Plazl, *Lab Chip*, 2009, **9**, 3385; (*f*) P. Znidarsic-Plazl and I. Plazl, *Process Biochem.*, 2009, **44**, 1115; (*g*) F. Benito-Lopez, R. M. Tiggelaar, K. Salbut, J. Huskens, R. J. M. Egberink, D. N. Reinhoudt, H. J. G. E. Gardeniers and W. Verboom, *Lab Chip*, 2007, **7**, 1345; (*h*) O. Naef, M. Roch and T. Chappuis, *Chimia*, 2010, **64**, 889; (*i*) J. Jovanovic, W. Hengeveld, E. V. Rebrov, T. A. Nijhuis, V. Hessel and J. C. Schouten, *Chem. Eng. Technol.*, 2011, **34**, 1691.