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Alkylation of carboxylic acids in a microfluidic device: kinetics parameters determination, Hammett reaction constant measurement and optimization of preparative experiment.

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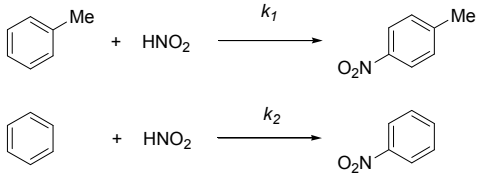
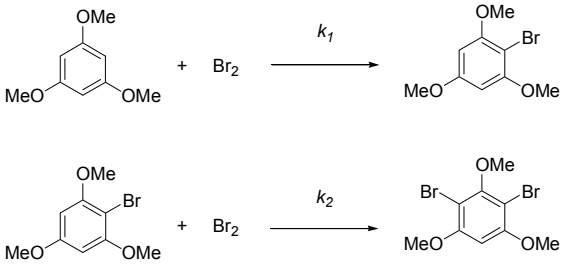
Abstract: A new proton sponge 1,8-bis(tetramethylguanidino)naphthalene (TMGN) was utilized for the alkylation of benzoic acid by iodomethane in a continuous flow microsystem. Using this set-up, kinetics of the reaction was determined in different mixing strategies and the Hammett reaction constant was measured. Good performance and efficiency of this procedure were confirmed through several preparative studies.

Introduction:

Chemical reactions are usually achieved by mixing of reagents or reagents/catalysts.[1] "Mixing" is a broad, generic term, which in a solution phase is defined as a phenomenon that creates homogeneity of all species in the solution. This is true if the mixing time is much shorter than the reaction time. In other words, if reaction is slower than mixing, the reaction proceeds in a homogeneous solution.[1] But there are some exceptions. Table 1 displays some mixing-sensitive reactions. Meanwhile, in general, decreasing the total mixing time to a level well below the time scale of the chemical reaction, is necessary to avoid the adverse effects of imperfect mixing on conversion and selectivity.[2] A facile technique for increasing the rate of mixing is to employ narrow, high aspect ratio reaction channels, hence increasing the interfacial surface area. During the current decade, the emergence and the development of microreactor technology offer to the synthetic chemists, innovative and alternative methods for mixing reagents with a better control on reactivity and selectivity. If extraordinary effects of such microreactor technology have been reported so far in synthetic chemistry, most of the fundamental physical and chemical phenomenons involved in such micro-devices, responsible of such reactivity, have now to be quantified or/and elucidated.

Table1. Types of mixing-sensitive reactions[3]

Competitive reactions	**Competitive-Consecutive reactions**
$A + B \rightarrow P_1$ $C + B \rightarrow P_2$ The ratio P_1/P_2 is lower, when mixing is slower than the reaction	$A + B \rightarrow P_1$ $P_1 + B \rightarrow P_2$ The yield of P_1 can be increased by faster stirring
Example :	**Example:**
	

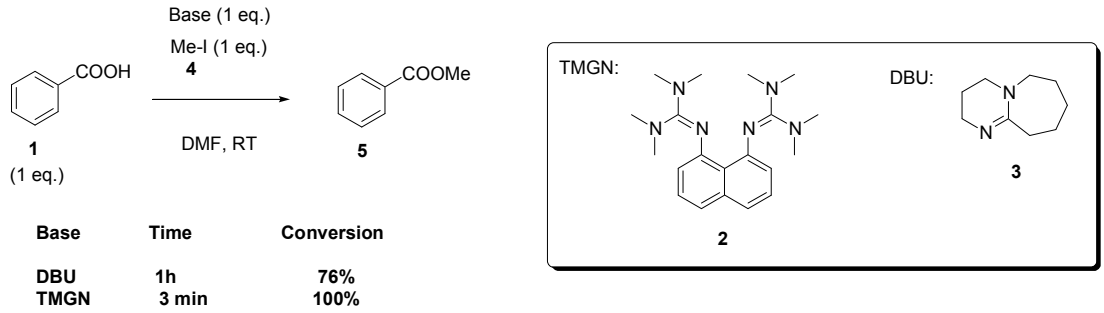
On the other hand, transformation of carboxylic acids into the corresponding methyl esters is a popular and fundamental process in organic synthesis and many methods have been developed for it. But usually these processes are time consuming and can take from 1.5 h to 24 h. There are several reports on esterification of benzoic acid under basic conditions, using 1,8-diazabicyclo [5.4.0]-undec-7-ene (DBU) as the base and various alkylating reagents. Such alternative method appears to be milder and extremely versatile compared to classical esterification procedures. Ono *et al.*[4] studied the reaction of benzoic acid and iodoethane in benzene and they reported a yield of 95% after 1.5 h. Later, Mal *et al.*[5] extended the procedure to iodomethane for the *O*-methylation of various carboxylic acids, under such conditions, the reaction time has been increased to 4 h.

In the course of a study, in the field of organic chemistry within microreactors, we recently focused on direct esterification of carboxylic acids in basic medium. Such chemical strategy, avoiding any dangerous or toxic pre-transformation of the carboxylic acid prior to use, represents a key challenge for the development of a more sustainable esterification method. In the present study, we envisage, for benzoic acid *O*-methylation, to evaluate a new proton sponge base, the 1,8-bis(tetramethylguanidino)naphthalene (TMGN), scheduled to be kinetically performing.[6, 7] More than defining new and competitive esterification conditions in batch we also envisage to transpose this reaction to microflow, by first focusing on the development of a new methodology for the measurement of kinetics rate constants within a modular microreactor. Then by comparison with a more classical batch version we intend to evaluate its implications as a new tool in organic chemistry. So we have determined the reaction rate constant for the esterification of different substituted benzoic acids by iodomethane under basic conditions. In this way, we have utilized a micromixer combined with a tubular reactor. Using the obtained rate constants data the Hammett reaction constant, ρ, has been determined. The measurement of ρ value is of particular importance for the elucidation of reaction mechanism and the prediction of many reaction characteristics such as selectivity. Finally, we have also, applied our developed procedure and set-up to do preparative experiments, using syringic acid (3,5-dimethoxy-4-hydroxybenzoic acid) to produce corresponding methyl esters quantitatively.

Results and discussion

Preliminary batch ^{1}H NMR studies

Benzoic acid **1** alkylation by MeI **4** in the presence of TMGN **2** was monitored, by ^{1}H NMR spectroscopy *in situ* using DMF-*d7* as solvent (scheme 1). We used equimolar quantities of benzoic acid **1**, TMGN and MeI **4** at a concentration of 0.2 mol.l^{-1}. We were delighted to observe the formation of methyl ester **5** in nearly quantitative yield during three minutes, while using TMGN **2**. This first study in batch demonstrated that TMGN is an extremely efficient base for the alkylation of benzoic acid. In order to compare this result to classical and moderately slow conditions based on the use of DBU, the same reaction in the presence of DBU was evaluated. After a reaction time of 1 h, the conversion determined by ^{1}H NMR was only 76%, demonstrating this important kinetics effect of TMGN on the reaction.



Scheme 1. Benzoic acid alkylation: comparative study between TMGN and DBU.

To the best of our knowledge, so far, these esterification conditions are the fastest ever evaluated. This type of extremely fast reaction can be considered has reviewed recently by Yoshida as a "Flash reaction" and could be easily transposed under microflow within a microreactor device.[8, 9]

Microsystem experimental set-up

To explore the potential of benzoic acid alkylation under microflow we set-up a modular microfluidic device composed of two streams of reagents simultaneously delivered to a micron scale mixer (mixing unit) followed by a fused silica-based capillary (residence time unit) in which the reaction is done (a schematic diagram of the experimental setup is given in Fig. 1). Numerous modifications can be realized on this system in order to vary critical reaction parameters, like: the internal diameter and the length of the capillary tubing in order to vary the residence time, the nature of the micromixer in order to evaluate different geometries and mixing configurations. In the present study, various microchannel dimensions (internal diameter, length) have been evaluated and compared. In such modular device, decreasing the internal dimensions of the system results in higher pressure drops, in order to vary easily the dimensions of the system and to evaluate every

possible configuration, a multi feeding high pressure syringe pump has been used for the introduction of the different reagents into the micromixer unit.

The mixing unit in the system can be easily modulated, we used an advanced multilaminating micromixer chip (NanoMixer®, Upchurch) and two different Tee junctions (Upchurch). One of these Tee junctions differing from the other by an internal frit unit supposed to increase the mixing properties.

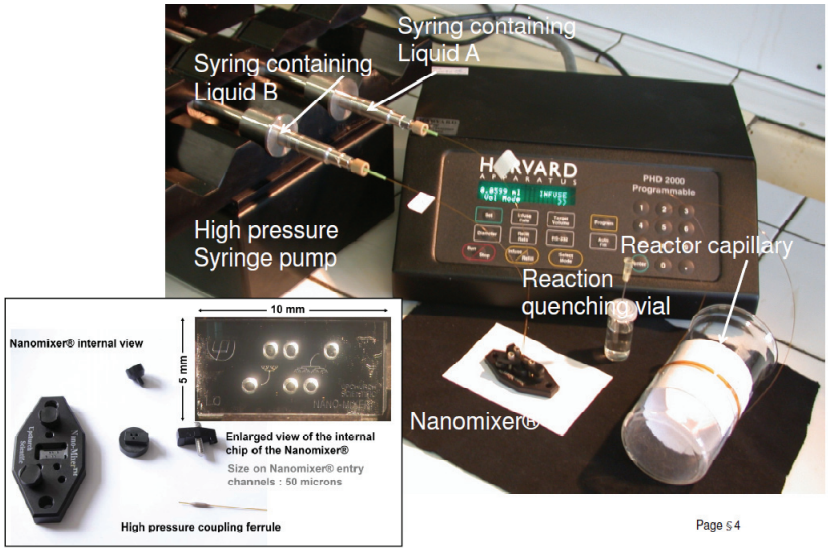


Figure 1. Experimental setup: schematic diagram of the experiment setup and the layout of the NanoMixer®.

The NanoMixer® consists of two inlets, the microchannel cascades, and one outlet, which operate in co-current flow mode. The layout of the micromixer is based on the principle of distributive mixing (Fig. 1). The microchip is made up from a glass/silicon/glass sandwich. On the silicon wafer, the inlet channel of liquid A is split into 16 partial flows. This is achieved by repeated splitting of the channels in such a way that an array of symmetrical elements results. On the backside of the silicon wafer (layer 2), liquid B is split into the same number of partial flows by an identical arrangement. In order to bring the two liquids together, liquid B is introduced to layer 1 *via* a number of wafer-through nozzles. Coming out of a nozzle, liquid B is allowed to develop into the full vertical height of the channel before it enters a channel with liquid A. Sequentially combining two neighboring channels into one is repeated until all partial flows are united in one broad outlet channel [10]. The mixture is then introduced into the tubular flow reactor. The final product can be collected and quenched at the tubing outlet and later analyzed by GC-MS or ^{1}H, ^{13}C NMR.

Analysis procedure for kinetics experiments

Analysis of reaction products was performed by GC/MS. To control the system performance, two internal standards, 1,3,5-trimethoxybenzene(TMB) and 1,4-dimethoxybenzene (DMB), were dissolved in liquid A and liquid B, respectively. Iodoanisole is another internal standard which was added to the samples, just before being analyzed by GC.

Table 2. Precision of the GC/MS method for the internal standards in one of the experiments with microsystem (Fourteen independent measurements, corresponding to the flow rates of 7.5 µl.mn^{-1} to 150 µl.mn^{-1}, TMB and DMB concentrations are 0.0036 and 0.0047 mol.l^{-1})

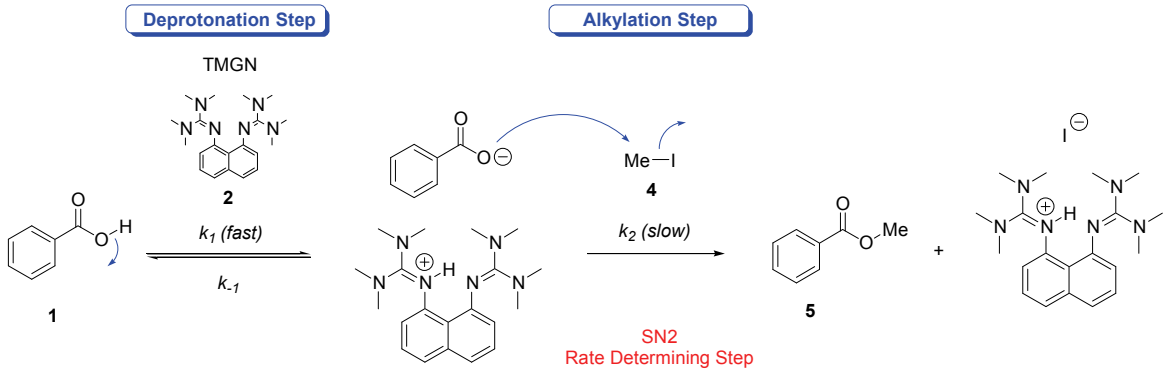
	TMB	DMB	Iodoanisole	TMB / TMB+DMB	DMB / TMB+DMB
Average peak area	1694267	1258007	1015225	0.6	0.4
Standard deviation (%)	5.3	4.7	6.0	0.7	0.9

To validate the precision of GC/MS analysis the peak areas of internal standards were integrated. The peak area ratio of each internal standard to the sum of both internal standards peak areas was calculated in the analyzed residence time intervals. It was also investigated by calculating the relative standard deviation (RSD) at all of our analyzed samples. This statistical analysis for one of our experiments has been displayed in Table 2. The absolute RSD of all the three internal standards compounds was less than 6% and less than 1% for their relative RSD. Furthermore this analytical method allowed us to use concentrations as low as 1 µmol.l^{-1}.

Analysis of reaction products was performed by GC/MS. GC/MS has been demonstrated to be a very sensitive and reproducible method. The main advantage of GC-MS is the spectral confirmation of each peak. With GC-MS, it was possible to identify all constituents of sample, internal standards, reagents and products, in a single run. Also, as other advantages of technique, we can mention ability of detecting trace amounts of chemicals, good precision and high accuracy.

Kinetics parameter determination in batch

The extraordinary speediness of the reaction directed us toward a precise kinetics study in batch, in order to confirm a second order kinetics as scheduled by the supposed two steps mechanism in which the first step corresponds to a preliminary deprotonation of benzoic acid followed by its alkylation by iodomethane as the rate determining step (Scheme 2).



Scheme 2. SN_2 mechanism of alkylation of benzoic acid by iodomethane using TMGN as base.

The mechanism of this reaction involves the deprotonation of benzoic acid to form benzoate anion, which behaves as a substrate for further alkylation by MeI, which is the rate determining step. Indeed the pK_{BH+} of TMGN in acetonitrile is estimated to be 25.1.[6] pK_a in DMF-dimethyl sulfoxide (DMSO), and DMSO-acetonitrile (ACN) and are related by equations (1) and (2) :

$$pK_a^{DMF} = 1.56 + 0.96\ pK_a^{DMSO} \quad (1) \qquad pK_a^{ACN} = 12.4 + 0.80\ pK_a^{DMSO} \quad (2)$$

By combining equations (1) and (2) equation (3) is obtained which correlates pK_a in DMF with pK_a in acetonitrile (ACN):

$$pK_a^{DMF} = -13.94 + 1.2\ pK_a^{ACN} \quad (3)$$

Therefore, pK_{BH+} of TMGN in DMF is estimated to be around 16.3. So TMGN is able to deprotonate totally the less acidic benzoic acids in DMF such as *para*-aminobenzoic acid the pK_a of which in DMF is 14.0.[11] So a clean second order kinetics is expected.

In all of our experiments the initial concentrations of benzoic acid and of iodomethane have been equal. Then the reaction rate can essentially be written as:

$$-\frac{d\ C_{BZA}}{dt} = kC_{BZA}^2 \quad (4)$$

where, k is the rate constant for the reaction and C_{BZA} is the concentration of benzoic acid.

After integration,

$$\frac{1}{C_{BZA}} - \frac{1}{C_{BZA_0}} = kC_{BZA_0}t \quad (5)$$

where C_{BZA_0} is the initial concentration of benzoic acid. However the parameters that can be determined easily experimentally are C_{BZA} the concentration of benzoic acid and C_{BZAMe} the concentration of benzoic acid methyl ester. Assuming $C_{BZA_0} = C_{BZA} + C_{BZAMe}$ and calling f the conversion

$$f = \frac{C_{BZAMe}}{C_{BZA} + C_{BZAMe}} \quad (6)$$

equation (5) may be expressed as (7) in which only appear the experimental value f and the initial concentration of benzoïc acid:

$$\frac{1}{1-f} = kC_{BZA_0}t + 1 \quad (7)$$

The straight line observed for 1/(1-conversion) = f(t) kinetics *vs* time (Fig. 2), clearly confirms that the reaction is second order with respect to benzoic acid and iodomethane.

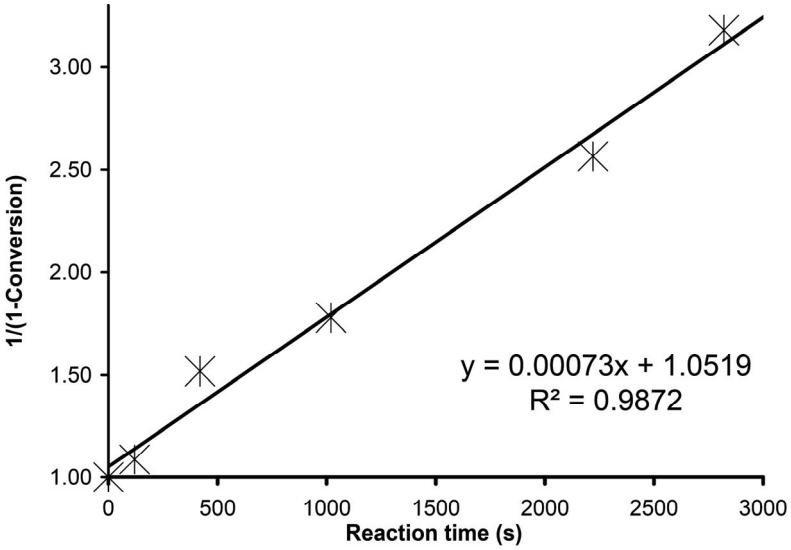


Figure 2. Plot of 1/(1-conversion) *vs*. time confirms that the reaction of benzoic acid with iodomethane in basic conditions follows second order kinetics in batch mode.

The mechanism clearly confirmed, we then decided to transpose this kinetics study from batch to microflow in order to define the basis of a versatile kinetics measurement methodology.

Kinetics measurement under microflow

Kinetics measurement within a microreactor is not trivial; indeed in such device, the time value differs from batch and corresponds to the residence time (reaction time inside the microchannel starting from the outlet of the micromixer). Since, there are in our modular microfluidic system, only two inlet flows, but three main reactants; it is possible to have three possible combinations for introducing the reagents into the micromixer unit. Contrary to the other bases like DBU, the kinetics of alkylation of TMGN by MeI in DMF is slow.[12] Therefore, it is possible to mix them, without any special problem. A summary of their obtained k values, as well as, that of a batch experiment are presented in Table 3.

Table 3. The summary of kinetics studies results in microsystem and in batch[a]

Liquid A	**Liquid B**	**C_B×1000 [mol.L^{-1}]**	**TMGN/BZA molar ratio**	**MeI/BZA molar ratio**	**Conv. %**	**k×10 [mol^{-1}.l.s]**
Benzoic acid, TMGN	MeI	2.81	1.0	1.0	61[a]	3.49
Benzoic acid	MeI, TMGN	2.20	1.1	1.0	51[a]	3.73
Benzoic acid MeI	TMGN	2.80	1.0	1.0	64[a]	5.21
Batch		2.35	1.0	1.0	44[a]	3.11

[a] Internal diameter and the length of the capillary 200 µm and 400 cm respectively
[b] The conversion is given for a residence or reaction time of 1257 s

The data plotted in Figure 3 are based on the obtained kinetics data for the first entry in Table 3 in which the benzoate preformed by putting together benzoic acid and TMGN (liquid A) is mixed with MeI (liquid B) both in DMF. Our kinetics study in microsystem again shows a second order mechanism for short time as expected but furthermore the reaction follows a second order kinetics up to a quantitative yield. For this reaction which is not very fast at these concentration (0.02 $mol.l^{-1}$), the kinetics constant is approximately equal in batch and in the microsystem as it may be expected. As pointed out previously TMGN and specially protonated TMGN is not alkylated by methyliodide in DMF at room temperature. So the two other possible combinations benzoic acid and MeI (liquid A) mixed with TMGN (liquid B) and benzoic acid alone (liquid A) mixed with MeI, TMGN (liquid B) gave almost the same kinetics constant.

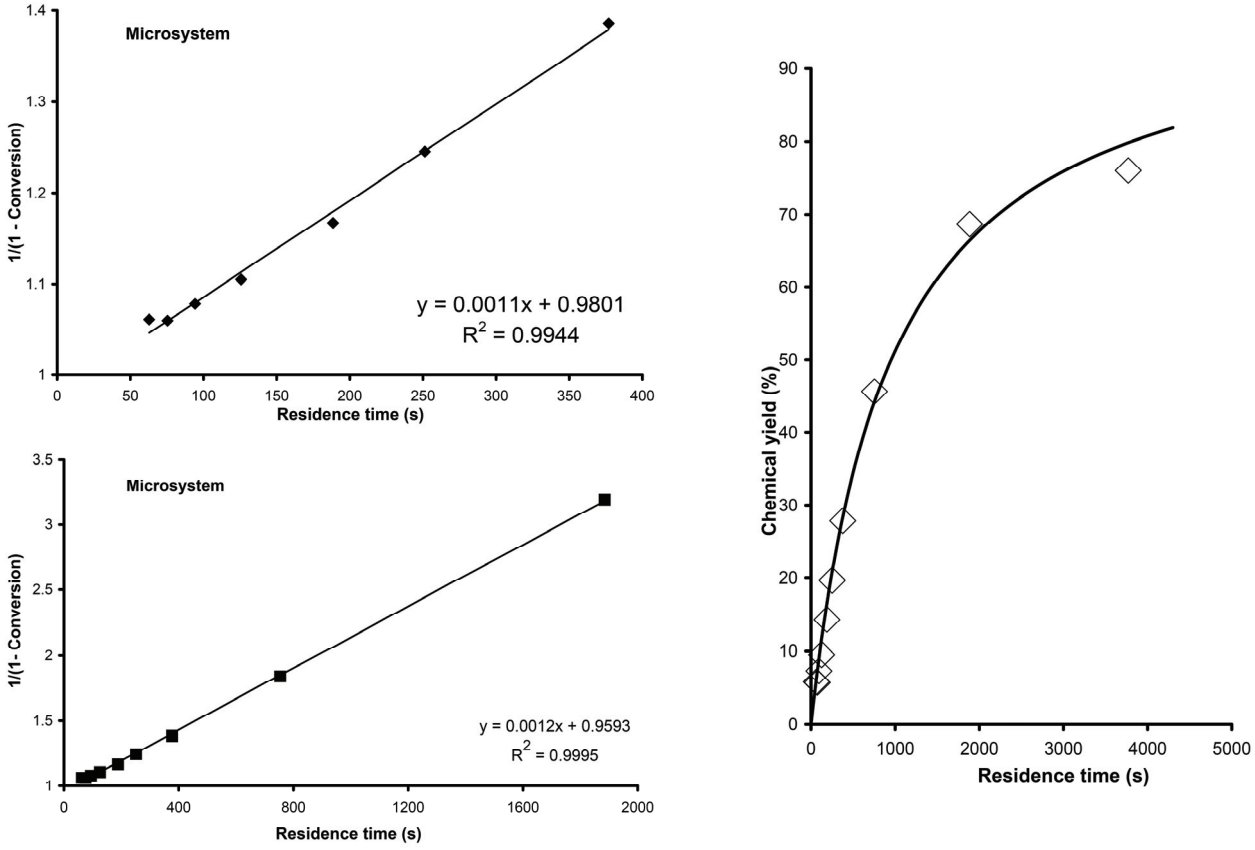


Figure 3. Plot of chemical yield *vs*. residence time shows that the reaction of benzoic acid with iodomethane in basic conditions goes on up to quantitative yield (right panel). Plot of 1/(1-conversion) *vs.* residence time confirms that the reaction of benzoic acid with iodomethane under basic conditions follows second order kinetics within microreactor at short time (upper left panel) but also long time (lower left panel).

Effect of experimental parameters on the relative reactivity

Numerous parameters can be changed on this system such as the internal diameter and the length of the capillary reactor. It is also possible to choose another type of micromixer. In the present study, we firstly investigated the effect of the capillary tube diameter and length, choosing a couple which keep the reactor volume constant, and so gave a constant residence time for a given flow rate. For this purpose, we compared a capillary with a diameter of 75 µm and length 3000 cm with one of diameter 200 µm and length 40 cm. In these experiments, liquid A was a solution of carboxylic acid and base in DMF and liquid B was solution of MeI in DMF. A brief summary of the obtained results for these experiments have been brought in Table 4. In this table, the conversion is given for the flow rate of 7.5 µl per minute. As it is observed the conversion is slightly higher within the smaller diameter capillary. More effective mixing in the radial direction by decreasing the diameter can be considered as a reason for the slightly higher reactivity in the smaller capillary.

Table 4. The effect of capillary reactor size in microsystem experiments

Internal diameter (µm)	Length(cm)	C_B×1000 [mol.l^{-1}]	TMGN/BZA molar ratio	MeI/BZA molar ratio	Conv. %[a]	k×10 [mol^{-1}.l.s]
75	300	20.88	1.1	1.0	49	8.62
200	40	22.62	1.1	1.0	57	5.79

[a] Conversion is for a residence time of 106 s

In order to estimate the quality of the mixing we tested the same two configurations in more stringent kinetics conditions by multiplying the methyl iodide concentration by ten (figure 4) compared to the value of Table 4. In those conditions assuming a first order reaction, rate constant $k_{First\ order}$ equals $0.862 \times 0.239 = 0.206\ s^{-1}$ and the half-live of the reaction is estimated to be 3.62 s using the 75 µm capillary. For comparison the axial mixing time for a small organic molecule (assuming a diffusion coefficient D = $5.00\ 10^{-10}\ m^2.s^{-1}$) in a 75 µm capillary is 5.6 s and 40 s in the 200 µm capillary.

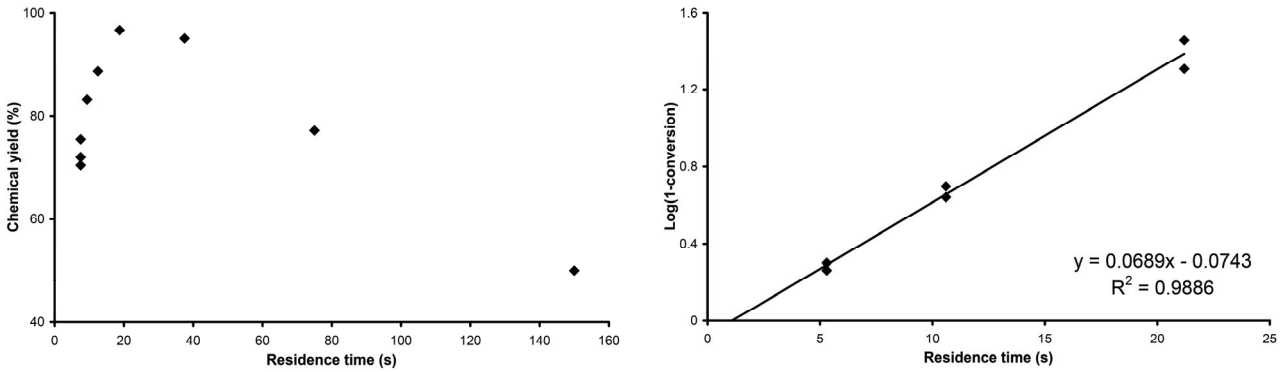


Figure 4. (Left panel) Conversion versus flow rate (µl.s^{-1}); (right panel) fit of the two parts of the curve according to first order law (log (conversion) versus residence time).

From the left panel in figure 5 it can be observed that the yield steadily increased when the flow rate is decreased until a maximum value near 100% and at flow rate lower than 20 µl.s^{-1} the yield decreases sharply. This decrease may be attributed to a non efficient mixing at low flow rate. The right panel in figure 4 shows that both part of the curve may be fitted by first order kinetics law even at time equal to the diffusion time. The calculated first order rate constant $k_{First\ order}$ is 0.07 s^{-1}, about one third of the expected value. This result shows that even at high flow rate the mixing is less than perfect.

Linear free-energy relationship for substituent effect:

A practical and reproducible method for kinetics measurements under microflow in hand, we then envisaged to determine the reaction rate Hammett constant for the esterification of different *para*-substituted benzoic acids by iodomethane within a microsystem based on Nanomixer® chip. In this way, the same procedure as the one used for the comparison with batch has been applied to other substituted benzoic acids. The effect of substituted reactant is expressed by the Hammett equation:[13]

$$\log {}^{k_x}/_{k_H} = \rho\sigma \tag{8}$$

where k_H is the rate constant for benzoic acid reaction, k_X he rate constant for substituted benzoic acid, ρ and σ are Hammett reaction and substituent values respectively. The measurement of ρ value is of particular importance for the elucidation of reaction mechanism and the prediction of many reaction characteristics such as selectivity.

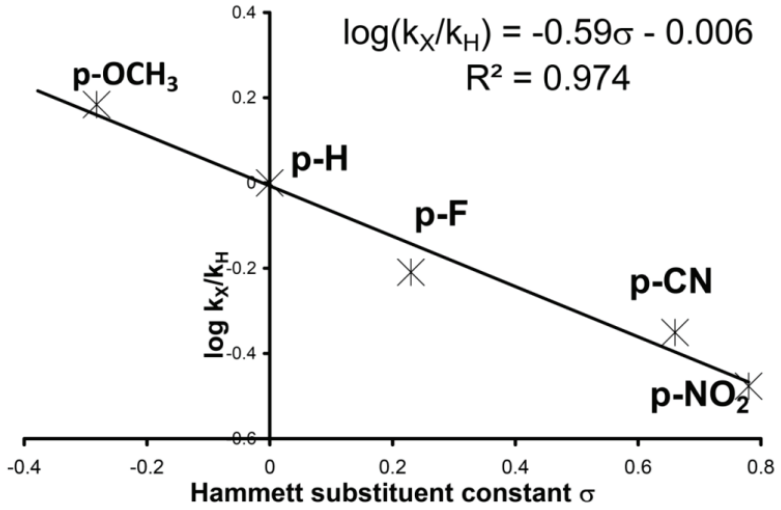


Figure 5. Plot of logarithmic rates for the reaction of iodomethane with substituted benzoic acids within microsystem.

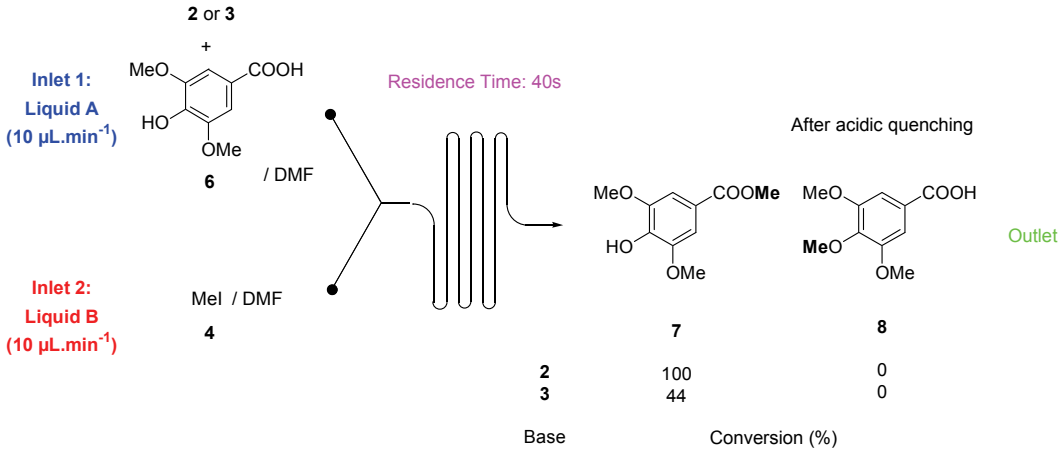
To measure the value of ρ, we did several experiments using different substituted benzoic acids and each time the value of $\log(k_x/k_H)$ was determined by the measurements of the formation of products. In these experiments, liquid A was a solution of carboxylic acid and base in DMF and liquid B was solution of MeI in DMF.

The Hammett plot is shown in Fig. 5. The obtained ρ value is -0.59. Kondo *et al*[14] have already reported the value of -0.92 for alkylation of substituted *tetra*-methylammonium benzoate with MeI in

acetonitrile. This higher value for the Hammett reaction constant may be accounted by two phenomena acting in the same way: the better solvatation of ion pairs in DMF than in acetonitrile and the higher reactivity of methyl iodide compared to ethyl iodide which make the reaction less sensitive to substituent effects as the reactivity is greater.

Preparative experiments

To do further investigation, the kinetics of the alkylation of syringic acid (3,5-dimethoxy-4-hydroxybenzoic acid) using either TMGN or DBU was also studied and some preparative experiments were also tried. Syringic acid is of particular interest since it contains, potentially, two reactive centers that may be alkylated. The reaction is shown by Scheme 3. For these studies, a mixture of syringic acid and MeI in DMF and a solution of base in DMF were used as liquid A and liquid B respectively.



Scheme 3. Preparative experiments with syringic acid under microflow.

The final step in the preparative experiments is to recover the sample from a large volume of quenching solution. In order to assess the chemical yield of the reaction the extraction procedure of a submilimolar mixture of syringic acid, methyl 3,5-dimethoxy-4-hydroxybenzoate **7**, and 3,4,5-trimethoxybenzoic acid **8** was tested on a sample containing a the same amount of each compound. Using acidic washing solution and dichlorometane as the extraction solvent a nearly quantitative recovery was observed. A careful inspection of ^{13}C NMR spectrum of the extract showed that the acid phenol **6**, the phenol methyl ether **8** and the ester **7** were quantitatively recovered. Using either DBU or TMGN, the hydroxyl phenol functional group is not alkylated and only the ester was obtained. The pKa of the carboxylic acid and of the phenolic group in DMF can be estimated by using a Hammet for correlating the acidities in DMF from data Maran *et al*[15] to be respectively (σ = = -0.13; pK_a^{DMF} = 18.5) and (σ = = -0.12; pK_a^{DMF} = 12.6). So it is expected that the 6 order of difference in acidity selectively orientates the reaction toward the formation of the methyl ester **7** exclusively. Meanwhile the reaction kinetics with TMGN is 12 times faster than with

DBU. In these conditions the obtained conversion, when using TMGN was around 100%, while using DBU leads to a conversion of less than 50% during the same duration.

Conclusion

1,8-bis(Tetramethylguanidino)naphthalene (TMGN) was demonstrated to be an excellent base for the alkylation of benzoic acid by iodomethane. This new flash reaction can be transposed in a continuous flow microsystem and result in an increased kinetics rate compared to a batch protocol. Using this microreactor set-up, it is possible to measure Hammet reaction constant directly under microflow. Variation of modular parameters demonstrated that modifications of the microchannel dimensions can affect the kinetics rate of the reaction under microflow. A preparative study focusing on the selective esterification of syringic acid under microflow confirmed that TMGN is much more effective as the base than DBU. Further studies concerning other applications of this new methodology will be reported in due course.

Experimental Section

General Information

All the experiments were performed at room temperature. All carboxylic acids, except 4-cyanobenzoic acid, 4-nitrobenzoic acid and 4-hydrobenzoic acid (Aldrich), were purchased from Alfa Aesar (a Johnson Matthey Company). All other chemicals except DMF (Fluka), iodomethane (Fluka) and BSTFA (Supelco) were obtained from Aldrich. All the chemicals were used as received.

The high pressure syringe pump (PHD 22/2000Hpsi) was a product of Harvard Apparatus (Les Ulis, France). Capillary tubes were purchased from Polymicro Technologies. NanoMixer® was purchased from Upchurch.

Chromatograms and mass spectra were collected using a Thermoscientific® gas chromatograph equipped with a PolarisQ® mass detector and EC®-1000 (30m×0.25mm) or Rtx®-5MS (60m×0.25mm) column. A linear temperature program was adapted to separate the different components depending on an initial temperature of 50 °C, and then a ramp of 10 °C/min, up to 250 °C. Helium (He) was the carrier gas at a flow rate of 1.0 ml/min. The mass spectra were recorded within 40–400 (m/z), full scan mode that revealed the total ion current (TIC) chromatograms. ^{1}H NMR and ^{13}C NMR experiments were performed with a Bruker (Wissembourg, France) Avance 300 Ultrashield spectrometer at room temperature in DMSO-d^6 and DMF-d^7 with calibration on the solvent peak. Chemical shifts are given in δ and coupling constants in Hz.

Kinetics study under microflow – General procedure

For the study of reaction kinetics, every reagents benzoic acids, methyl iodide and TMGN were dissolved in DMF (16 ml, 0.02 mol.l^{-1}) prior to use, flow rates (and residence time) were varied. Each time, for taking sample, 240 µl of reaction medium was collected at the outlet of the tubular reactor and quenched in a mixture of 400 µl of dichloromethane and 50 µl of formic acid. For each flow rate, two samples were taken directly and analyzed independently. A volume of 30 µl of the taken sample was diluted by 400 µl of

iodoanisole in dichloromethane solution. This sample, is later derivatized by 50 µl of BSTFA and 20 µl of pyridine and was kept overnight for further analysis.

For the study of reaction kinetics, all the reactants in one syringe were dissolved in 8 ml of DMF To change the residence time flow rates were varied. Each time, for taking sample, 240 µl of reaction medium was collected at the outlet of the tubular reactor and quenched in a mixture of 400 µl of dichloromethane and 50 µl of formic acid. For each flow rate, two samples were taken directly and analyzed independently. A volume of 30 µl of the taken sample was diluted by 400 µl of iodoanisole in dichloromethane solution. This sample, is later derivatized by 50 µl of BSTFA and 20 µl of pyridine and was kept overnight for further analysis.

Preparative study – General procedure

In preparative experiments, a mixture of syringic acid (94-96 mmol.l^{-1}) and MeI (153-161 mmol.l^{-1}) in DMF and a solution of base (159 mmol.l^{-1}) in DMF were used as liquid A and liquid B respectively. The flow rate was constant, at 20 µl per minute, all through the experiment. For these experiments, the internal diameter and the length of the capillary were 75 µm and 300 cm respectively.

The outlet flow was quenched in a solution of 1:10 by volume of formic acid in distilled water. We used a procedure of three times successive washing with 30 ml of dichloromethane and consecutively washing the separated organic phase three times ,each time with 10 ml of HCl (1 mol.l^{-1}). The final product was obtained by evaporation of the solvent. This product was analyzed through ^{13}C NMR spectra.

NMR assignments.

Syringic acid (**6**): ^{1}H NMR (DMSO-*d*^{6}, 300MHz): δ (ppm) 3.35 (1H), 3.80 (s, 6H), 7.19 (s, 2H), 9.23 (s, 1H).^{13}C NMR (DMSO-*d*^{6}, 300MHz): δ (ppm) 166.27, 147.42, 140.16, 120.35, 106.79, 55.96, 51.90.

Methyl 4-hydroxy-3,5-dimethoxybenzoate (**7**): ^{1}H NMR (DMSO-*d*^{6}, 300MHz): δ (ppm) 3.81 (s, 9H), 7.21 (s, 2H), 9.36 (s, 1H). ^{13}C NMR (DMSO-*d*^{6}, 300MHz): δ (ppm) 166.12, 147.54, 140.60, 119.17, 106.65, 56.019, 51.90.

3,4,5-trimethoxybenzoic acid (**8**): ^{1}H NMR (DMSO-*d*^{6}, 300MHz): δ (ppm) 3.72 (s, 6H), 3.82 (s, 3H), 7.23 (s, 2H), 12.97 (s, 1H). ^{13}C NMR (DMSO-*d*^{6}, 300MHz): δ (ppm) 166.96, 152.66, 141.33, 125.93, 106.51, 60.12, 55.92.

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