CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200700331

Reaction Rates as a Function of Scale within Ionic Liquids: Microscale in Droplet Microreactors versus Macroscale Reactions in the Case of the Grieco Three-Component Condensation Reaction

Philippe Dubois,[a, b] Gilles Marchand,*[a] Said Gmouh,[b] and Michel Vaultier*[b]

Abstract: Task-specific ionic liquids (TSILs) and more specifically binary task-specific ionic liquids (BTSILs), a unique subclass, have been shown to be excellent supports for solution-phase chemistry. The negligible volatility of ionic liquids enables their use as stable droplet microreactors in atmospheric environments without oil protection or confinement. These droplets can be moved, merged and mixed by electrowetting on a chip. Solution-phase synthesis can be performed on these open digital microfluidic labs-on-a-chip as illustrated by a study of the Grieco three-component reaction in [tmba]-[NTf$_2$]-droplet (tmba = N-trimethyl-N-butylammonium NTf$_2$ = bis(trifluoromethylsulfonyl)imide) microreactors. A detailed study of matrices and scale effects on conversion and kinetic rates of this three-component condensation is presented in this paper. Reactions have been shown to be slower in droplets than in batches in the absence of additional mixing. Also, a significant influence of the ionic-liquid matrix has been observed. Finally, an increase of droplet's temperature resulted in a kinetics enhancement so as to reach macroscale reaction rates, probably because of a much better mixing of reaction's components involving a Marangoni's effect.

Keywords: Grieco reaction · ionic liquids · kinetics · microreactors · reaction scale effects

Introduction

During the past ten years, ionic liquids, particularly room-temperature ionic liquids (RTILs), have attracted considerable attention. Due to their negligible vapour pressure, they are considered "greener" alternatives to volatile organic solvents. Numerous applications of ionic liquids as non-aqueous polar alternatives in biphasic systems, like extraction solvents[1] or electrolytes,[2] have been reported. They are also used in transition-metal or enzymatic catalysis[3] and especially in organic synthesis.[4–7] Indeed, in this last case, several authors reported the effect of ionic liquids on the stereoselectivity or reactions kinetics.[8,9] One of the most recent developments is the use of task specific ionic liquids (TSILs) as soluble supports, therefore expanding their potential applications far beyond those of conventional ionic liquids. Indeed, by grafting of a functional group either to the cation or the anion of an ionic liquid, one can confer special chemical properties to an onium salt and serve as a reagent or reactant. These TSILs[10–13] possess all ionic liquid advantages and can be used as templates for supported organic synthesis in solution. Besides offering a nice alternative to solid-phase-supported synthesis, the advantages are numerous because reactions are carried out in homogeneous mixtures thus recovering liquid-phase characteristics. Moreover, high-melting, functionalised onium salts can be used as solutions either in non-functionalised ionic liquids (binary task specific ionic liquid; BTSIL)[14] or molecular solvents. These reagents have already been successfully used for peptides synthesis,[15,16] multicomponent reactions,[12,13,17] pericyclic reactions, such as cycloadditions,[14,18] and transition metal-catalysed reactions.[19]

Recently, labs-on-a-chip (LOC) dedicated to chemical applications have attracted growing interest.[20–24] Indeed, compared to a traditional batch reaction, miniaturised systems allow reducing the consumption of reagents, faster optimisation of reactions and production of the desired products usually in greater yield and purity. Moreover, LOC minimise waste production and increase the security during the dan-

---

[a] P. Dubois, Dr. G. Marchand
CEA Léti-MINATEC
Department of Technology for Biology and Health
17 rue des Martyrs 38054 Grenoble (France)
Fax: (+33) 438-785-787
E-mail: gilles.marchand@cea.fr

[b] P. Dubois, Dr. S. Gmouh, Dr. M. Vaultier
University of Rennes 1, UMR CNRS 6510
263 Avenue du Général Leclerc, 35042 Rennes cedex (France)
Fax: (+33) 223-236-955
E-mail: michel.vaultier@univ-rennes1.fr

gerous synthesis, as they dissipate efficiently heat generated by exothermic reaction owing to their high surface-area to volume ratios.

Microsystems usually consist of a network of micron-sized channels embedded into a solid substrate. However, in spite of many advantages, these microsystems suffer from several drawbacks, such as large dead volumes, frequent obstruction of the channels, difficulties to maintain a constant hydrodynamic pressure (especially for viscous liquids) or to control surface charges when electro-osmotic pumping is used. In an attempt to avoid these problems, Zheng and Ismagilov[25] have described a continuous-flow microfluidic system in which droplets are separated by liquid spacers involving complex protocols to work with these systems. This approach consists of an array of nanoliter plugs of many different reagents, separated and surrounded by a fluorinated carrier fluid and gas bubbles inside a hydrophobic glass or plastic capillary.

To overcome all these difficulties, it has been proposed[26,27] that droplets containing reagents, samples, and so forth, could be displaced on two-dimensional chips (as opposed to microfluidic channels) by various fluidic actuators such as acoustic waves or, more often, electrowetting on dielectric (EWOD). Thus, after merging of droplets, a chemical reaction occurs within the resulting droplet acting as a microreactor. Such droplet microfluidic systems have several advantages as complex fluidic connections and associated problems (as previously described) are avoided. Furthermore, this digital[28] approach gives great flexibility in the creation and handling of droplet microreactors.

Recently, several authors[29,30] described the actuation and the displacement of ionic liquids by EWOD and we reported the use of this technology to create a chemical microprocessor.[31] In our study, we explored the possibility of using droplets of RTILs and TSILs as stable microreactors, on an open digital microfluidic chip by using EWOD as the fluidic actuator. A supported version of the Grieco three-component condensation[32] in droplets affording tetrahydroquinolines, an important class of biologically active compounds,[33] was performed on such a microsystem.

In this paper, we describe the influence of the matrix solvents and scales (micro versus macro) on the conversion and kinetics rates of the TSIL-supported version of the Grieco three-component condensation reaction. These studies allowed for a selection of the most adapted ionic liquids and reaction conditions to perform the reaction in droplet microreactors as efficiently as in batches reactors.

Results and Discussion

As described in a previous paper,[31] a droplet of ionic liquid containing different reagents can be easily displaced by EWOD on a silicon chip under air. In summary, the EWOD technology is based on the observation that an electrical field modifies the contact angle of a conducting droplet on a hydrophobic substrate. This principle is described by the Lippmann-Young equation [Eq. (1)] and was first reported by Berge:[34]

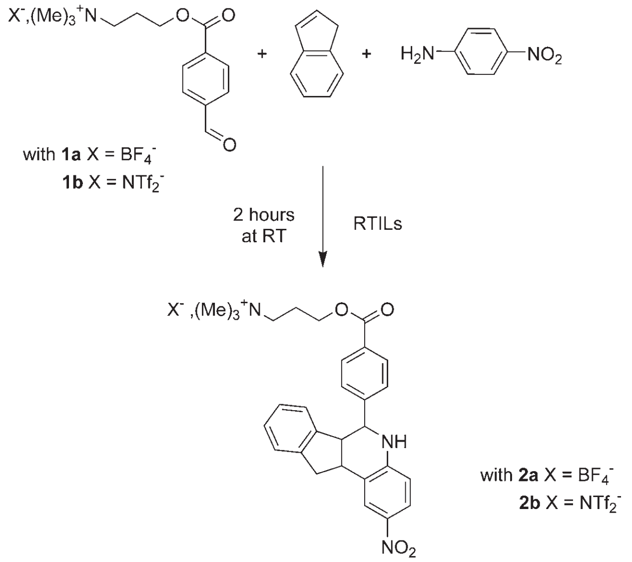
$$\cos\theta = \cos\theta_0 + 0.5\,CV^2/\gamma_{\mathrm{LG}} \qquad (1)$$

In Equation (1) θ_0 is the natural contact angle, θ is the contact angle when the electric field is actuated, C is the capacitance per surface unit of the layer between the electrodes and the liquid, V is the applied voltage and γ_{LG} is the surface tension between the drop and the surrounding fluid (air or insulating liquid).

The actuation generates a spreading of the droplet on the hydrophobic surface and then a sequential actuation of neighbouring electrodes on the chip permits a displacement of the droplet.[35–37]

Thus, we demonstrated the possible use of EWOD technology for the easy handling of droplets of reagents or TSILs or onium salts dissolved in RTILs matrices and the efficient completion and monitoring of Grieco's multicomponent reaction.[31] This reaction is a well-known three-component condensation that occurs rapidly at room temperature in volatile organic solvents (VOS) with a quantitative yield and has been demonstrated on solid supports.[38] This reaction consists of the condensation of an aniline, an aldehyde and an electron-rich olefin in the presence of an acidic catalyst and occurs by means of an aza-Diels–Alder type reaction. We showed the feasibility of such a reaction with a quantitative conversion rate after incubation for one hour at room temperature in a 0.6 µL droplet of [tmba][NTf_2] (tmba = *N*-trimethyl-*N*-butylammonium NTf_2 = bis(trifluoromethylsulfonyl)imide).

In this paper, we describe a study of the influence of the matrix solvents and scale on this Grieco condensation (Scheme 1) in terms of conversion and kinetic rates. Thus, the reaction was first performed in macroscopic scale in dif-



Scheme 1. Schematic representation of the Grieco's reaction on task-specific onium salts in different RTILs ([tmba][NTf_2], [bmim][BF_4], [bmim]-[PF_6], [tbma][NTf_2], [bmim][NTf_2] and [bmp][NTf_2]).

ferent RTILs. In our experiments, the task-specific onium salt **1** was dissolved in different solvents (RTILs), then 2.5 equivalents of *p*-nitroaniline, 4 equivalents of trichloroacetic acid (TCA), an internal reference (see Experimental section), and an excess of indene, were successively added to this solution. All the reactions developed in batch were next transposed to droplet format. Three droplets, containing the previous reagents in same proportions (see Experimental Section) and dissolved in the same solvents as for bulk scale, were merged by EWOD at 55 V_{rms} on our chip. During the incubation, sampling was performed and the extracted samples were analysed by ESI-MS and HPLC. To quantify the reaction, an HPLC method using the internal reference was applied, as described in our previous paper[31] to avoid a conversion rate determination blemished with errors, especially when microvolumes are used. Note that, if one single batch can provide HPLC with enough samples to follow the reaction's kinetics, seven reactions leaded in parallel, in droplet format, were needed to get enough samples for HPLC analysis.

Matrix effects: Firstly, macro- and microscale reactions were studied in different solvents, all proceeding smoothly at ambient temperature, in order to observe the influence of matrix solvents (Figure 1). Hence, this first criterion allows for selecting the most adapted RTILs to perform droplet reactions.

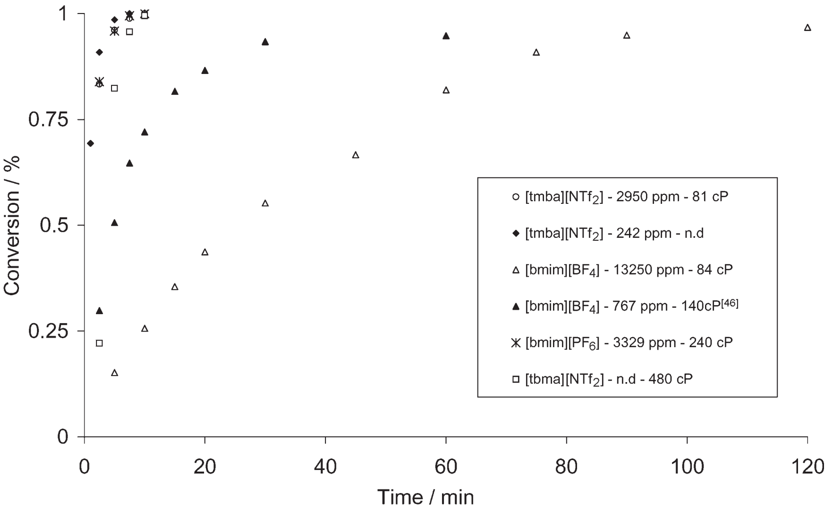


Figure 1. Reaction kinetics for the Grieco reaction in different ionic liquids in batch format. Water content was measured by injection of the RTILs dissolved in methanol in a coulometric Karl Fisher titrator (GRScientific). For all curves, the absolute error ΔT on the measurement was between 7 and 10 depending on the conversion rate V, following the equation $\Delta V = 0.04\,\mathrm{V}(1+\frac{\sqrt{2}}{V})$. The dynamic viscosity (η in cP) was calculated after measurement of the kinematic viscosity with Ubbelholde (Schott) micro-viscosimeter at 20 °C.[46]

In macroscopic format (Figure 1), a total conversion was observed after 5–7 minutes of reaction in [tmba][NTf$_2$] or [bmim][PF$_6$] (bmim = 1-butyl-3-methylimidazolium). A longer time (10 minutes) was necessary in [tbma][NTf$_2$] (tbma = *N*-tributyl-*N*-methylammonium) to reach complete conversion, because of the very high viscosity of this ionic liquid ($\eta = 480$ cP). In the same way, the observed kinetics in [bmim][BF$_4$] were much slower than in the other ionic liquids, as 90 minutes were necessary to reach 95 % conversion. Firstly, this phenomenon can be explained by the high water content in [bmim][BF$_4$] due to the hygroscopic character of this ionic liquid. To verify this hypothesis, [bmim][BF$_4$] was dried under vacuum at 70 °C for 2 h, during which time the water content decreased from 13250 to 767 ppm. With this dried ionic liquid, the necessary time to reach a 95 % yield was divided by three. However, the water content cannot be the only explanation, since no influence of water was observed when the reaction was performed in [tmba][NTf$_2$] containing either 2950 or 242 ppm of water. Furthermore, the Grieco reaction can be performed in water.[39] So, the hydrolysis of the BF_4^- ion generating fluorohydric acid could explain the influence of water content. Indeed, the F^- ion can serve as counterion for the iminium intermediate, leading to a stable complex that would reduce the rate enhancement. This hypothesis has been verified by adding a solution of tetrabutylammonium fluoride in THF (1 M, 10 µL) to [tmba][NTf$_2$] (1 mL). A decrease of the reaction rate was observed leading to a longer time (15 minutes) to reach a 100 % rate conversion. Another explanation could be that the polymerisation of indene acts as a competitive reaction catalysed by the Lewis acid BF_3,[40] generated during the hydrolysis of the BF_4^- ion.

At the microscopic scale (Figure 2), the reaction kinetics and the conversion rates appear similar in [tmba][NTf$_2$], [bmim][NTf$_2$] and [bmp][NTf$_2$] (bmp = 1-butyl-1-methylpyrrolidinium). All these ionic liquids present comparable viscosities and contain the NTf_2^- hydrophobic ion. In the case of [tbma][NTf$_2$], the slower rate observed is due to its higher dynamic viscosity, as observed in the batch format. Surprisingly, low reaction kinetics and very small conversion rates were observed with [bmim][BF$_4$] and [bmim][PF$_6$] as solvents. Thus, conversion rates of 5 and 20 % were estimated in [bmim][BF$_4$] and [bmim][PF$_6$], while complete conversions rates were observed in batch after 2 h and 7 min, respectively. The viscosity could partially explain this result. However, a fast kinetic and a high conversion rate were obtained in [tbma][NTf$_2$] with a 480 cP viscosity as compared to [bmim][BF$_4$] with $\eta = 84$ cP. Here again, like in batch format, the BF_4^- hydrolysis generating F^- in the reaction mixture could be involved. However, in contrast to

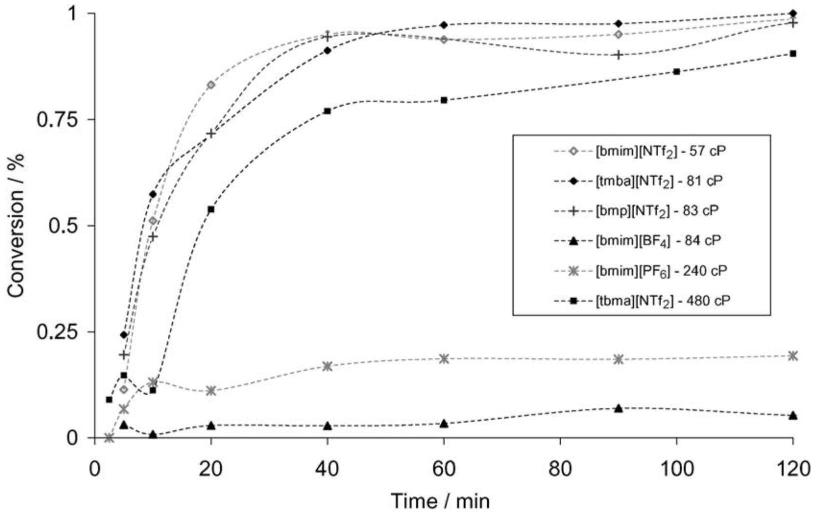


Figure 2. Conversion rates for the Grieco reaction in different ionic liquids in droplet format. The dynamic viscosity (η in cP) was calculated after measurement of the kinematic viscosity with an Ubbelholde (Schott) micro-viscosimeter at 20°C. Dotted lines have no physical meaning, but allow only a better visualisation. As noted above, each point on the above curves corresponds to a single microreactor, which explains the variation while complete conversion is obtained. Absolute error is between 7 and 10% as in Figure 1.

what has been observed in the macroscopic scale, the reaction is much slower in the microscopic format in [bmim][PF$_6$] as solvent. PF_6^- hydrolysis might occur as well, as reported in the literature,[41,42] favoured by a high surface/volume ratio in the droplet format. The F^- ions generated from the PF_6^- can perturb the reaction, following the same processes as for BF_4^-. Moreover, in the droplet format, as the mixing is only provided by diffusion (see the section on scale effects), competitive reactions can occur since the Grieco reaction is slowed down.

Finally, we investigated the influence of the replacement of the BF_4^- ion in the onium salt **1** by a NTf_2^- ion on the Grieco reaction in [tmba][NTf$_2$]. No significant effects on the kinetics and conversion rates were observed at macro- and microscales when shifting from one anion to the other. Thus, it seems that the nature of the supporting salt anion has no or very slight influence on the Grieco reaction rate.

On the basis of this preliminary study on the influence of the matrix, we chose [tmba][NTf$_2$] as the ionic liquid matrix for the scale effects study.

Scale effects: As shown in Figures 1 and 2, a 100% conversion rate was observed with [tmba][NTf$_2$] after 2 h in the two formats. However, we generally observed a lower rate in droplets than in batches whatever the solvent used. It could be related to reagents mixing problems in the droplets for which only diffusion is operating. We attempted to improve the rate enhancement of Grieco's reaction in [tmba][NTf$_2$] in droplet format by improving mixing.

Firstly, after merging, one should displace droplets back and forth on the chip. However, even if the mixing of aqueous solutions is improved by using this method,[43] this technique was ineffective with RTILs. Indeed, as shown in Figure 3A, the mixing of one droplet (0.2 µL) of [tmba][NTf$_2$] containing a fluorescent molecule and one without is really low. After merging and one cycle of back and forth displacement on the chip, the fluorescent droplet goes back close to its original position. A homogeneous solution was obtained only after several cycles of back and forth displacement (about 6 minutes later).

An explanation of this poor mixing rate can be been obtained from the Reynolds number [Eq. (2)]. In this equation u is the speed of the droplet, l is the diameter of the droplet and ν is dynamic viscosity of the RTIL.

$$\mathrm{Re} = u\,l/\nu \qquad (2)$$

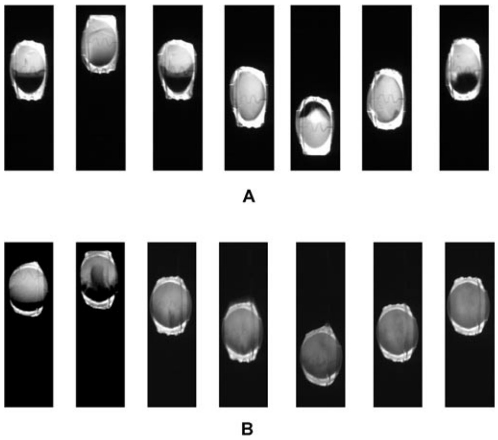


Figure 3. Pictures showing the mixing of a droplet of [tmba][NTf$_2$] containing a fluorescent probe with another droplet of pure [tmba][NTf$_2$]. A) Mixing at room temperature after one cycle of back and forth displacement. B) Mixing with underneath heating (120°C) after one cycle of back and forth displacement.

This number characterises the ratio between the inertia forces (ul) and the viscosity forces (ν) applied on a system, and consequently the mixing (the higher the Reynold's number, the better the mixing). The maximum speed reached by a droplet of [tmba][NTf$_2$] on our chip is about 1.3 mm s^{-1} for a dynamic viscosity of 81 cP. Therefore, the Reynolds number for the mixing of two 0.2 µL droplets of [tmba][NTf$_2$] is 3×10^{-2}. This very low Reynolds number shows that for ionic liquids, inertia forces are negligible as compared to viscosity forces and is characteristic of a creeping system (as opposed to turbulent or laminar),[44] which is clearly disadvantageous for a quick mixing.

In a second approach, heat resistance was used to heat the ionic liquid droplets from underneath during their displacement. As shown in Figure 3B, a quick mixing was observed due to an important internal flow. The experiment was repeated at 40, 80 and 120 °C and always led to a quick mixing (2 min at 40 °C and less than 20 s at 80 and 120 °C). This improvement of the mixing could be due to the decrease of the viscosity of the RTIL with the increase of temperature and/or to the contribution of a Marangoni effect.[45]

Performing a Grieco reaction in using the heating mixing method, as shown in Figure 4, led to a rate enhancement with the increase of temperature.

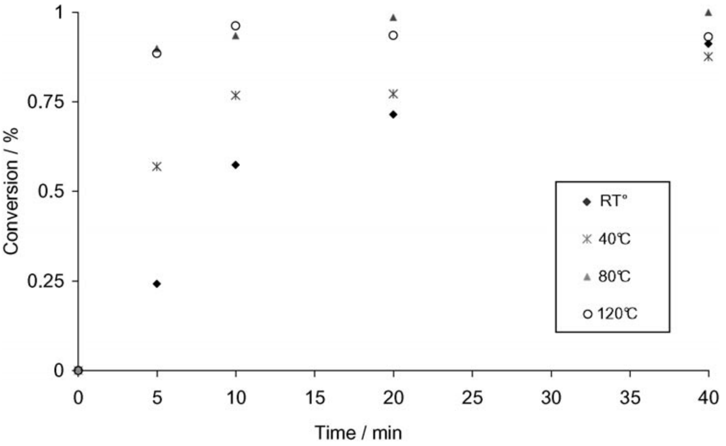


Figure 4. Reaction kinetics for the Grieco reaction in [tmba][NTf$_2$] droplets at different temperatures. As in Figures 1 and 2, absolute errors are between 7 and 10%.

Thus, a nearly complete conversion was observed after 10 min at 80 °C or 120 °C, whereas 40 min at ambient temperature are necessary to obtain the same result. We assume that this rate enhancement is likely to be due to the improvement in the droplets mixing and not to a temperature effect on the Grieco reaction rate, since it is fast at ambient temperature in the macroscale. Currently, we are working on an additional agitation of droplets and evaluating its effect on conversion rates.

Conclusion

In summary, this paper shows that for a given reaction, that is, the Grieco three-component condensation reaction, and a given ionic liquid, the reaction is faster in the batch scale than in microscale, that is in droplets microreactors. A detailed study of ionic liquids matrixes and scale effects on conversion and kinetics rates has been presented. The slow reaction observed in droplets in the absence of additional mixing can be circumvented by increasing the droplets' temperature so as to reach the macroscale reaction rate. The viscosity of the ionic liquids matrices related to the anion nature and the amount of water present was shown to be determinant. Hydrolysis of BF_4^- and PF_6^- ions liberating F^- in the reaction mixtures also seems to play some role.

Experimental Section

RTILs: 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF$_4$]), 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF$_6$]), tri-*N*-butylmethylammonium bis(trifluoromethylsulfonyl)imide ([tbma][NTf$_2$]) and 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide ([bmp][NTf$_2$]) are commercially available from Merck KGaA and Solvionic SA and were used without further purification. The other ionic liquids were synthesised according to protocols developed in our laboratory.

1-Butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim]-[NTf$_2$]): Freshly distilled 1-methylimidazole (8.21 g, 0.1 mol) was mixed, under argon, with 1-chlorobutane (1 equiv, 9.26 g) in a sealed flask, which was then heated up to 70 °C for 3 days. After cooling, the product was washed with hot ethyl acetate (3×20 mL). The salt was purified by recrystallisation in a 1:1 mixture of acetonitrile/ethyl acetate to give a white powder (14.1 g). This product (8.725 g, 0.05 mol,) was dissolved in water (75 mL). Powdered lithium bis(trifluoromethylsulfonyl)imide (15.77 g, 0.055 mol) was added to the mixture. The ionic liquid immediately separated from the aqueous phase. After decantation and washing with distilled water, the ionic liquid (20.5 g) was dried under vacuum for several hours at 60 °C. Yield: 98%. ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 0.96$ (t, $J = 7.3$ Hz, 3H), 1.30 (m, 2H), 1.95 (m, 2H), 4.02 (s, 3H), 4.32 (t, $J = 7.3$ Hz, 2H), 7.70 (m, 2H), 8.94 ppm (s, 1H); ^{13}C NMR (50.32 MHz, [D$_6$]acetone): $\delta = 13.6$, 19.9, 32.7, 36.6, 50.3, 119.7 (q, J-(C,F) = 321.2 Hz), 123.4, 124.8, 137.3 ppm; HRMS(FAB) for $(2C^+, NTf_2^-)^+$: *m/z* calcd: 558.1643; found: 558.1640; elemental analysis calcd (%) for $C_{10}H_{15}F_6N_3O_4S_2$: C 28.64, H 3.61, N 10.62, S 15.29; found: C 28.57, H 3.85, N 10.02, S 15.13.

***N*-trimethyl-*N*-butylammonium bis(trifluoromethylsulfonyl)imide ([tmba][NTf$_2$])**: In a sealed flask, trimethylamine (2 equiv, 45 wt% aqueous solution) and the minimum volume of acetonitrile to obtain a monophasic reaction medium were added to chlorobutane (1 equiv). The flask was heated up to 70 °C for overnight. After elimination of volatiles and solvents under vacuum, the residue was washed with diethyl ether and recrystallised from acetone leading to a white solid. It was dissolved in the minimum of distilled water and lithium bis(trifluromethylsulfonyl)imide (1.1 equiv). The two water solutions were mixed. After 2 h of stirring at room temperature, the [tmba][NTf$_2$] was extracted with methylene chloride and this last solution dried over Na_2SO_4. The solvent was removed under vacuum giving a water-like free-flowing liquid that was dried under high vacuum at 60 °C for 3 h. Yield: 85%; ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 0.95$ (t, $J = 7.31$ Hz, 3H), 1.40–1.59 (m, 2H), 1.88–2.11 (m, 2H), 3.42 (s, 9H), 3.60–3.75 ppm (m, 2H); ^{13}C NMR (75 MHz, [D$_6$]acetone): $\delta = 14.1$, 20.6, 25.8, 53.9 (t, J(C,N) = 4.1 Hz), 67.7, 121.8 ppm (q, J(C,F) = 321.0 Hz); ^{19}F NMR (376 MHz, [D$_6$]acetone): $\delta = -80.3$ ppm; HRMS(FAB) for $(2C^+, NTf_2^-)^+$: *m/z* calcd: 512.2051; found: 512.2069; elemental analysis calcd (%) for $C_9H_{18}F_6N_2O_4S_2$: C 27.27, H 4.58, N 7.07, S 16.18; found: C 27.27, H 4.90, N 7.20, S 16.03.

Starting reagents

[3-(4-Formylbenzoyloxy)propyl]trimethylammonium tetrafluoroborate (1a): In a sealed flask, trimethylamine (2 equiv, 45 wt% aqueous solution) and the minimum volume of acetonitrile in order to obtain a monophasic reaction medium were added to 1-chloropropan-3-ol (1 equiv). The flask was heated up to 70 °C overnight. After elimination of volatiles and solvents under vacuum, the residue was washed with diethyl ether and recrystallised from acetone leading to a white solid. *N*,*N'*-Dicyclohexylcarbodiimide (1.5 equiv), 4-carboxybenzaldehyde (1.5 equiv) and 4-dimethylaminopyridine (0.02 equiv) were added to 3-hydroxypropyltrimethylammonium chloride (1 equiv) dissolved in acetonitrile (50 mL). The reaction was carried out in a flask at room temperature for 4 h. Solvents were removed by vacuum distillation and the ester was removed by washing with water. For the metathesis, HBF_4 (1.5 equiv, 50% water solution) were added to the previous ester and mixed for 2 h at room temperature. After filtration and evaporation of water, product **1** was obtained as a white solid. Yield: 90 %; ^{1}H NMR (200 MHz, [D$_3$]acetonitrile): δ = 2.10–2.33 (m, 2H), 3.05 (s, 9H), 3.36–3.55 (m, 2H), 4.45 (t, J = 5.8 Hz, 2H), 8.00 (dd, J = 1.6, 6.6 Hz, 2H), 8.13 (dd, J = 1.4, 8.3 Hz, 2H), 10.10 ppm (s, 1H); ^{13}C NMR (50 MHz, [D$_3$]acetonitrile): δ = 22.08, 52.66 (t, J = 3.8 Hz), 61.53, 63.52 (t, J = 3.0 Hz), 129.10, 129.80, 134.39, 139.27, 164.89, 192.04 ppm; ESI/MS for C$^+$: m/z calcd: 250.3; found: 250.2.

[3-(4-Formylbenzoyloxy)propyl]trimethylammonium bistrifluoromethylsulfonimide (1b): The protocol is the same as for **1a** except the anion metathesis step. After reaction and without purification, the metathesis was performed by adding powdered lithium bis(trifluoromethylsulfonyl)imide (1.5 equiv) and HCl (10 µL, 1 M) to the previous ester and mixed for 1 h at room temperature. After extraction with diethyl ether (3 × 30 mL) and washing with water, solvents were removed by vacuum distillation. The residue was then dissolved in methylene chloride and dried with potassium carbonate overnight at room temperature. After filtration, removing of solvents by vacuum distillation, the residue was dissolved in methylene chloride. Active charcoal was added into the solution and stirred overnight. After filtration over Celite, a yellow oil was obtained. Yield: 90 %; ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 2.54 (m, 2H), 3.45 (s, 9H), 3.89 (m, 2H), 4.54 (t, J = 5.7 Hz, 2H), 8.05 (d, J = 8 Hz, 2H), 8.20 (d, J = 8.3 Hz, 2H), 10.16 ppm (s, 1H); C NMR (50 MHz, [D$_6$]acetone): δ = 24.56, 54.80 (t, J = 3.8 Hz), 63.88, 65.88 (t, J = 3.0 Hz), 131.23, 131.93, 136.47, 141.63, 166.81, 197.70 ppm; ESI/MS for C$^+$: m/z calcd: 250.144; found 250.36; elemental analysis calcd (%) for $C_{16}H_{20}F_6N_2O_7S_2$: C 36.23, H 3.80, N 5.28, S 12.09; found: C 36.26, H 3.94, N 5.38, S 11.69.

Internal reference (fluorescent probe): In a sealed flask, Trimethylamine (2 equiv) were added to 1-chloro-propan-3-ol. The flask was heated up to 70 °C overnight. After elimination of volatiles and solvents under vacuum, the residue was washed with diethyl ether and recrystallised from acetone leading to a white solid. The white solid was then dissolved in acetonitrile, and bis(trifluoromethylsulfonyl)imide (1.2 equiv) dissolved in the minimum of water was added. After 2 h stirring at room temperature, the product was extracted with CH_2Cl_2. After evaporation of CH_2Cl_2, the obtained oil was washed with diethyl ether. The resulting alcohol (1 equiv) was dissolved in acetonitrile, dansyl chloride (1.1 equiv) dissolved in CH_2Cl_2 and K_2CO_3 (1.2 equiv) were added and the mixture stirred for 36 h at room temperature. After evaporation of organic solvents, the residue was washed with diethyl ether, and then with water. The internal reference (yellow solid) was obtained after high vacuum removal of residual solvents. Yield = 10 %; ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 2.35 (m, 2H), 2.93 (s, 6H), 3.37 (s, 9H), 3.64 (m, 2H), 4.21 (t, J = 5.22 Hz, 2H), 7.35 (d, J = 7.63 Hz, 1H), 7.65–7.80 (m, 2H), 8.28 (d, J = 8.58 Hz, 1H), 8.31 (d, J = 7.63 Hz, 1H), 8.72 ppm (d, J = 8.58 Hz, 1H); ^{13}C NMR (200 MHz, [D$_6$]acetone): δ = 23.03, 45.00, 53.10 (J(C,N) = 4.1 Hz), 63.5, 67.8, 116.1, 117.1, 119.2, 123.8, 129.2, 129.8, 131.0, 131.2, 132.0 ppm; ESI/MS for C$^+$: m/z calcd: 351.17; found 351.27; elemental analysis calcd (%) for $C_{20}H_{27}F_6N_3O_7S_3$: C 38.03, H 4.31, N 6.65, S 15.23; found : C 37.97, H 4.54, N 6.93, S 15.30; UV/fluorescence (2 × 6.10^{-5} mol L^{-1}, CH_3CN): λ_{abs} = 344 nm (ε = 3300 mol L^{-1} cm^{-1}); λ_{fluo} = 544 nm.

Grieco's Reaction

Macroscale: *p*-Nitroaniline (1.1 equiv), indene (10 equiv) and TCA (4 equiv) were added to **1a** or **1b** (1 equiv) dissolved in an RTIL matrix (2 mL). The reaction was kept at room temperature for 2 h with regular take off for reaction monitoring. Solvents were then removed under vacuum, and the solid residue was washed with diethyl ether.

Microscale: Seven 0.2 µL droplets of RTILs containing **1**, TCA (4 equiv) and internal reference (0.1 equiv) were deposited on an electrowetting chip and displaced by EWOD at 55 V. Each droplet converged towards a second droplet of ionic liquid containing *p*-nitroaniline (2.5 equiv). After coalescence, the resulting droplets were merged with a third droplet containing an excess of indene. During the incubation, the droplets have been sampled at different times, washed with diethyl ether to eliminate the excess of *p*-nitroaniline and indene and then analysed by HPLC.

To obtain the pure compounds **2a** and **2b**, the RTIL was replaced by CH_3CN in the macroscale protocol described above. After 2 h at room temperature, CH_3CN was then removed under vacuum, and the solid residue was washed with diethyl ether. After filtration and recrystallisation from pentane, the final product **2a** or **2b** was obtained.

Data for {3-[4-(2-Nitro-5,6*a*,7,11*b*-tetrahydro-6*H*-indeno[2,1-*c*]quinolin-6-yl)benzoyloxy]propyl}trimethylammonium tetrafluoroborate (2a): ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 2.28 (dd, J = 7.3, 14.9 Hz, 1H), 2.57 (m, 2H), 3.05 (m, 1H), 3.24 (m, 1H), 3.51 (s, 9H), 3.93 (m, 2H), 4.55 (t, J = 6 Hz, 2H), 4.69 (d, J = 7.3 Hz, 1H), 5.1 (m, 1H), 6.67 (s, 1H), 6.89–8.1 ppm (m, 11H); ESI/MS for C$^+$: m/z calcd: 486.23928; found 486.2384; ESI/MS^2 for C$^+$: m/z calcd: 427.166; found 427.36; ESI/MS^3 for C$^+$: m/z calcd: 369.124; found 369.18.

Data for {3-[4-(2-Nitro-5,6*a*,7,11*b*-tetrahydro-6*H*-indeno[2,1-*c*]quinolin-6-yl)benzoyloxy]propyl}trimethylammonium bistrifluoromethylsulfonimide (2b): Yellow solid; ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 2.28 (dd, J = 7.4, 14.9 Hz, 1H), 2.54 (m, 2H), 3.05 (m, 1H), 3.24 (m, 1H), 3.47 (s, 9H), 3.89 (m, 2H), 4.51 (t, J = 6 Hz, 2H), 4.66 (d, J = 7.6 Hz, 1H), 5.12 (m, 1H), 6.66 (s, 1H), 6.80–8.19 ppm (m, 11H); ESI/MS for C$^+$: m/z calcd: 486.239; found 487.09; ESI/MS^2 for C$^+$: m/z calcd: 427.166; found 428.27; ESI/MS^3 for C$^+$: m/z calcd: 369.124; found 370.18.

Fabrication of the device: In this technology, one wafer of silicon and one micro-structured metal layer are needed. After performing wet oxidation (2 µm) on the wafer, the gold electrodes (800 µm × 800 µm) were formed by deposition of a 5-nm layer of Cr and then a 300-nm layer of Au on the wafer followed by patterning using standard microfabrication techniques. Next, the wafer was coated with a 300 nm layer of silicon nitride (ε_R = 7.8) deposited by PECVD followed by an etching of this layer for electrical contact. After sawing off the wafer, an approximately 1 µm spin-coated layer of amorphous Teflon-AF-1601 (DuPont; ε_R = 1.9) was deposited on the chips.

Packaging of chips: The chips (8 mm × 6.5 mm) were glued on a PCB support and connected by wire bonding (gold wires 25 µm). The wire bonding machine was also used to create a network of thin metallic catenaries (25 µm) over the chip, required for EWOD actuation.

Instrumentation: The packaged chip was connected to electrical switches, driven by a computer that activated the different electrodes and controlled the displacement of droplets.

Acknowledgements

This work was supported in part by the Ministère de la Recherche. We thank the members of BIOSOC project (CEA/LETI) for their technical assistance. We also thank F. Vinet and Y. Fouillet (CEA/LETI), and M. Blanchard-Desce (University of Rennes 1) for helpful discussions.

---

[1] A. Visser, R. P. Swatloski, W. M. Reichert, R. Mayton, S. Sheff, A. Wierzbicki, J. H. Davis, Jr., R. D. Rogers, *Chem. Commun.* **2001**, 135 – 136.
[2] C. Lagrost, D. Carrié, M. Vaultier, P. Hapiot, *J. Phys. Chem. A* **2003**, *107*, 745 – 752.
[3] P. Lozano, T. De Diego, D. Carrié, M. Vaultier, J. L. Iborra, *Chem. Commun.* **2002**, 692 – 693.
[4] P. Wasserscheid, T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim (Germany), **2003**.
[5] R. D. Rogers, K R. Seddon, *Science* **2003**, *302*, 792 – 793.
[6] T. Welton, *Chem. Rev.* **1999**, *99*, 2071 – 2083.
[7] J. M. Fraile, J. I. Garcia, C. I. Herrerias, J. A. Mayoral, D. Carrié, M. Vaultier, *Tetrahedron: Asymmetry* **2001**, *12*, 1891 – 1894.
[8] M. J Earle, P. B. McCormac, K. R. Seddon, *Green Chem.* **1999**, *1*, 23 – 25.
[9] C. J. Adams, M. J. Earle, G. Roberts, K. R. Seddon, *Chem. Commun.* **1998**, 2097 – 2098.
[10] S. T. Handy, M. Okello, *J. Org. Chem.* **2005**, *70*, 2874 – 2877.

[11] A. E. Visser, R. P. Swatloski, W. M. Reichert, R. Mayton, S. Sheff, A. Wierzbicki, J. H. Davis, Jr., R. D. Rogers, *Environ. Sci. Technol.* **2002**, *36*, 2523–2529.

[12] M. Vaultier, S. Gmouh, French patent FR 2845084, Application 2002-11910, WO 2004029004.

[13] M. Vaultier, S. Gmouh, F. Hassine, French patent FR 2857360, Application 2003-8413, WO 2005005345.

[14] S. Lee, *Chem. Commun.* **2006**, 1049–1063.

[15] W. Miao, T. H. Chan, *J. Org. Chem.* **2005**, *70*, 3251–3255.

[16] C. Roche, A. Commerçon, M. Vaultier, French Patent, 0501557, filed up 02/16/2005.

[17] F. Hassine, Ph.D. Thesis, University Hassan II, Casablanca, Morocco, May **2005**.

[18] G. Silvero, M. J. Arevalo, J. L. Bravo, M. Avalos, J. L. Jimenez, I. Lopez, *Tetrahedron* **2005**, *61*, 7105–7111.

[19] J. M. Fraile, J. I. Garcia, C. I. Herrerias, J. A. Mayoral, D. Carrié, M. Vaultier, *Tetrahedron: Asymmetry* **2001**, *12*, 1891–1894.

[20] Y. Kikutani, H. Hisamoto, M. Tokeshi, T. Kitamori, *Lab Chip* **2004**, *4*, 328–332.

[21] D. M. Ratner, E. R. Murphy, M. Jhunjhunwala, D. A. Snyder, K. F. Jensen, P. H. Seeberger, *Chem. Commun.* **2005**, 578–580.

[22] G. N. Doku, W. Verboom, D. N. Reinhoudt, A. van den Berg, *Tetrahedron* **2005**, *61*, 2733–2742.

[23] S. Taghavi-Mogadam, A. Kleemann, K. G. Golbig, *Org. Process Res. Dev.* **2001**, *5*, 652–658.

[24] D. A. Snyder, C. Noti, P. H. Seeberger, F. Schael, T. Bieber, G. Rimmel, W. Ehrfeld, *Helv. Chim. Acta* **2005**, *88*, 1–9.

[25] a) B. Zheng, R. F. Ismagilov, *Angew. Chem.* **2005**, *117*, 17, 2576–2579; *Angew. Chem. Int. Ed.* **2005**, *44*, 2520–2523.

[26] T. Taniguchi, T. Torii, T. Higuchi, *Lab Chip* **2002**, *2*, 19–23.

[27] M. G. Pollack, A. D. Shenderov, R. B. Fair, *Lab Chip* **2002**, *2*, 96–101.

[28] J. Gong, S.-K. Fan, C.-J. Kim, *IEEE Int. Conf. Micro Electro Mech. Syst. Tech. Dig. 17th* **2004**, 355.

[29] S. Millefiorini, A. H. Traczyck, R. Sedev, J. Efthimiadis, J. Ralston, *J. Am. Chem. Soc.* **2006**, *128*, 3098–3101.

[30] D. Chatterjje, B. Hetayothin, A. R. Wheeler, D. J. King, R. L. Garrell, *Lab Chip* **2006**, *6*, 199–206.

[31] P. Dubois , G. Marchand, Y. Fouillet , J. Berthier, T. Douki, F. Hassine, S. Gmouh, M. Vaultier, *Anal. Chem.* **2006**, *78*, 4909–4917.

[32] P. Grieco, A. Bahas, *Tetrahedron Lett.* **1988**, *29*, 5855–5858.

[33] A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron* **1996**, *52*, 15031–15070.

[34] B. Berge, *C. R. Acad. Sci. Ser. II* **1993**, *13*, 157–163.

[35] T. B. Jones, *J. Micromech. Microeng.* **2005**, *15*, 1184–1187.

[36] F. Mugele, J. C. Baret, *J. Phys. Condens. Matter* **2005**, *17*, 705–774.

[37] Y. Fouillet, D. Jary, A. G. Brachet, C. Chabrol, J. Boutet, P. Clementz, D. Lauro, R. Charles, C. Peponnet, *Micrototal Analysis System 2005*, Boston (USA), **2005**, 59–62.

[38] A. Kiselyov, R. W. Armstrong, *Tetrahedron Lett.* **1997**, *38*, 6163–6166.

[39] G. Satori, F. Bigi, R. Maggi, R. Mazzacani, G. Oppici, *Eur. J. Org. Chem.* **2001**, 2513–2518.

[40] A. Mizote, T. Tanaka, T. Higashimura, S. Okamura, *J. Polym. Sci. Part A* **1966**, *4*, 869–879.

[41] G. Rangits, G. Petocz, Z. Berenet, L. Kolar, *Inorg. Chim. Acta* **2003**, *353*, 301–305.

[42] J. H. Davis, Jr., P. A. Fox, *Chem. Commun.* **2003**, 1209–1212.

[43] P. Y. Paik, V. K. Pamula, M. G. Pollack, R. B. Fair, *Lab Chip* **2003**, *1*, 28–33.

[44] E. M. Purcell, *Am. J. Phys.* **1977**, *45*, 3–11.

[45] J. J. Hegseth, N. Rashidnia, A. Chai, *Phys. Rev. E* **1996**, 54, 2, 1640–1644.

[46] K. R. Seddon, A. Stark, M.-J. Torres, *Pure Appl. Chem.* **2000**, *72*, 2275–2287.

Received: February 28, 2007