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Continuous Flow Production of Thermally Unstable Intermediates in a Microreactor with Inline IR-Analysis: Controlled Vilsmeier–Haack Formylation of Electron-Rich Arenes

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Supporting Information

ABSTRACT: The Vilsmeier–Haack formylation of aromatic compounds is a well-established process in organic synthesis, largely driven by the fact that the resulting aldehydes are generally useful intermediates for the synthesis of fine chemicals and pharmaceutical products. Industrial-scale production, however, is often hampered by laborious procedures requiring the use of hazardous chemicals to produce the highly reactive intermediates. In order to circumvent these issues, a flow chemistry approach was developed. This article describes the design and semiautomated optimization of the Vilsmeier–Haack formylation in continuous flow and subsequent scale-up to preparative volumes in an intrinsically safe manner.

1. INTRODUCTION

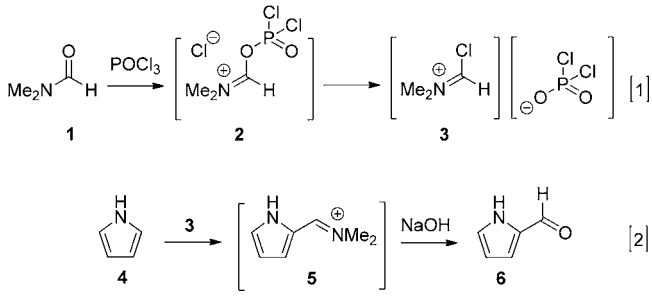
The methodologies developed throughout the years for formylation of aromatics are as numerous as they are diverse, indicating not only the intrinsic value of aromatic aldehydes as synthetic intermediates but also the lack of generally applicable routes to synthesize these aldehydes. Hence, a large variety of relatively specific syntheses are well-established; however, they appear rather laborious.[1−6] Moreover, hazardous chemicals are often required, rendering scaling up problematic.[7] The Vilsmeier–Haack (VH) reaction is nowadays frequently used for formylation of electron-rich arenes[8−12] and ketones,[13] and in addition is used in cyclohaloaddition,[14] cyclization reactions,[15] and ring annulations.[16] In the VH reaction a chloroiminium ion is formed as the reactive species by mixing a substituted amide with phosphorous oxychloride.[17] The highly electrophilic iminium ion then reacts with the arene, after which basic hydrolysis with sodium hydroxide leads to the aldehyde. Albeit that the intermediate chloroiminium ion can be readily prepared, calorimetric studies have demonstrated that its formation poses specific thermal hazards due to thermal instability and can generate high and fast temperature rises when heated, possibly resulting in a thermal runaway.[7] This requires active cooling, and the latter makes batchwise scale-up rather troublesome.[18] We envisioned that a flow chemistry approach would enable the VH formylation at industrial scale with enhanced safety, because in a microreactor the reaction takes place on a microliter scale, allowing excellent heat dissipation and thereby rendering active cooling of the system superfluous.

In 2010, Kim et al. briefly demonstrated the feasibility of VH formylation of *N*,*N*-dimethylaniline as a proof for their newly developed flexible polyimide (PI) film microreactor.[19] On the basis of these results, we decided to extensively investigate the opportunities for a widely applicable flow method for formylation of electron-rich arenes. Our approach involves inline formation of the formylating agent followed by the addition to the arene and hydrolysis to the aldehyde. The combined process has been validated by successful application to a series of substrates.

2. RESULTS AND DISCUSSION

We chose to investigate the formylation of pyrrole as a representative case for VH formylation in a continuous flow process (Scheme 1). In batch, 2-formylpyrrole (**6**) is prepared

Scheme 1. Vilsmeier–Haack formylation of pyrrole



in a three-step procedure, first allowing the chloroiminium ion **3** to be formed from DMF at low temperature, generally at 0 °C. In a second step, pyrrole is added at elevated temperatures (typically 60 °C), while in a third step the resulting iminium adduct **5** is hydrolyzed to give product **6** upon heating in a sodium acetate or sodium hydroxide solution.[20]

In a continuous flow process, using FutureChemistry's Flowstart B-200, DMF (**1**, syringe A) and phosphorous

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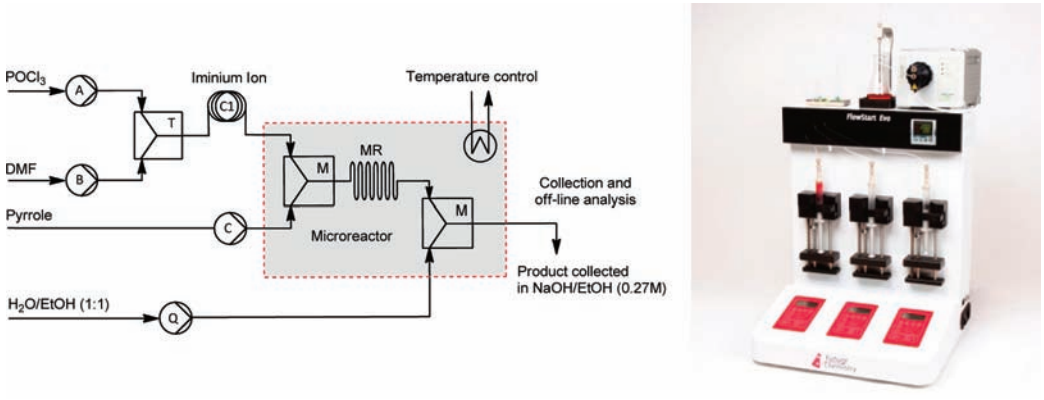

Figure 1. Schematic drawing of the microreactor setup.

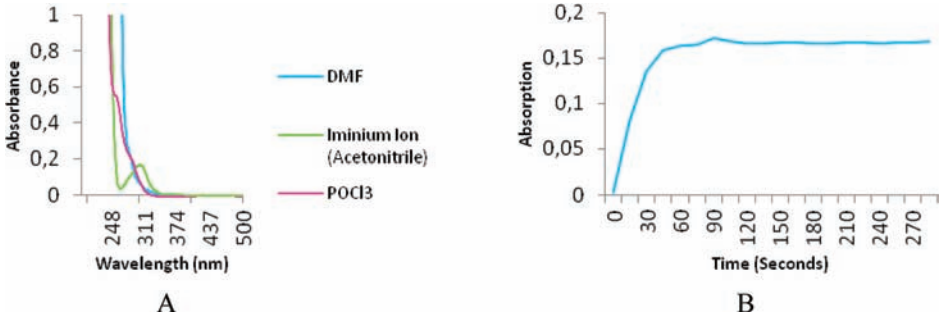

Figure 2. UV absorption spectra of the reaction species (A) and formation of the VH reagent in MeCN (B) at 304 nm.

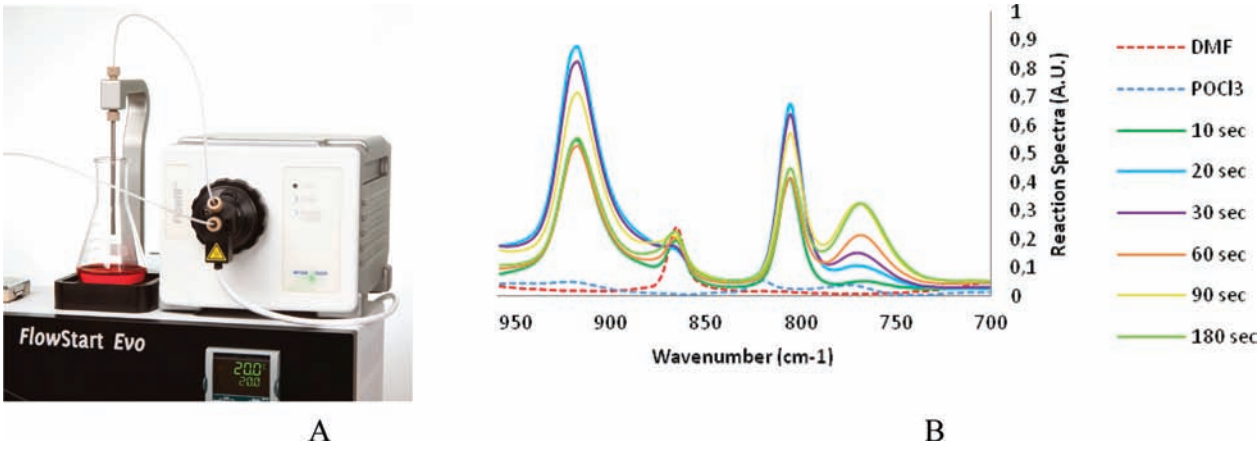

Figure 3. (A) Zoom-in of the Flowchemistry setup with the FutureChemistry FlowStart *Evo*[23] (B-400 and the Mettler Toledo Autochem FlowIR). (B) IR absorbance spectra showing the two main bands of interest at 769 cm^{-1} (C−Cl) and 804 cm^{-1} (P−O−C) changing as a function of residence time.

oxychloride ($POCl_3$, syringe B) were mixed using a T-splitter (T) and transferred into a coil (C1) to allow the chloroiminium ion (**3**, Vilsmeier−Haack reagent) to be formed. An excess of DMF was used to ensure full conversion of $POCl_3$ and to retain the intermediate in solution. The reactive intermediate **3** was then delivered at a constant flow rate into the temperature-controlled microreactor (MR) together with pyrrole and toluene (internal standard, syringe C) for the formylation reaction to proceed. Finally, the reaction was quenched with a mixture of H_2O and ethanol (syringe Q). In contrast to known procedures, as described in the previous section, the resulting iminium ion **5** was hydrolyzed in a solution of NaOH (0.27 M) and ethanol. Ethanol was added to ensure solubility of the internal standard (toluene), which is not necessary for a preparative-scale method. A schematic drawing of the microreactor setup is shown in Figure 1. The reactor has an internal volume of 92 μL, a channel width of 600 μm, a channel depth of 500 μm, and an effective channel length of 360 mm. The channel layout contains two additional mixing units (M) being of the folding flow type.[21] The reactor temperature was controlled by Peltier elements and sensed by a Pt1000 temperature sensor.

Initial experiments showed that it is critical to reach full conversion of $POCl_3$ in the coil, because it reacts vigorously with pyrrole to form polymers, thereby clogging the reactor. An atline spectrophotometric method was developed to determine the reaction time for inflow formation of the chloroiminium ion **3** at room temperature. Measuring the reaction time without

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solvent proved to be impossible, since DMF shows UV-absorbance around 300 nm; being used as a solvent, its UV absorbance overlaps with that of the iminium ion (Figure 2A). The absorbance was therefore measured at low concentrations of DMF, using acetonitrile as the solvent. Under these conditions, UV absorbance at a wavelength of 304 nm showed that formation of the chloroiminium ion **3** was completed within 90 s (Figure 2B).

The main issue we encountered during the UV measurements was the inability to perform real-time analysis of the unstable intermediate without the use of additional solvents (e.g., MeCN). This problem was thought to be overcome by connecting inline a Mettler Toledo FlowIR infrared flow cell[22] with the outlet of the microreactor.[22] The data obtained from this inline infrared analysis can provide insight not readily available from other sources.

In order to identify spectral bands unique to the intermediate species infrared spectra of both substrates DMF and $POCl_3$ were recorded using the FlowIR system. Next, the formation of the VH reagent was visualized by the relative intensity of a characteristic stretching vibration (C−Cl) at 769 cm^{-1} (Figure 3), measured at fixed reaction times. The results show an initially fast formation of the phosphonium salt **2** (green line, Figure 4), as identified by a characteristic bending frequency

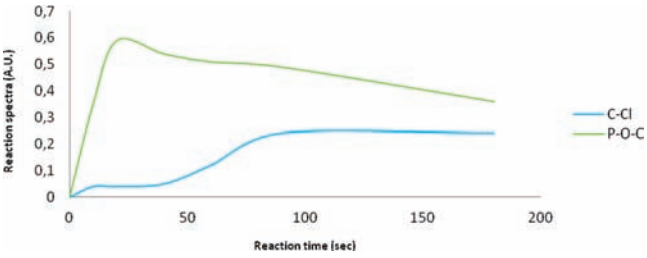

Figure 4. Reaction times for the formation of the phosphonium salt **2** and the VH reagent.

(P−O−C, 804 cm^{-1}). The formation of the Vilsmeier−Haack reagent **3** (blue line, Figure 4) shows a rapid increase between 50 and 100 s reaction time, which may be caused by increasing chloride concentration due to decomposition of the dichlorophosphate counterion of **3** (eq 1, Scheme 1). From these results, it was concluded that the formation of the VH reagent was completed within 90 s.

Next, a full optimization study[24−26] was designed on the basis of reaction time (t_r = 10, 30, 60, 120, 180, 300 s), temperature (T = 0, 20, 40, 60 °C), and molar ratio of $POCl_3$ to the pyrrole substrate (MR = 1, 2, 3, 4). All experiments were performed with a fixed reaction time of 90 s for the formation of the chloroiminium ion **3** unless stated otherwise. Even though the quench of the intermediate iminium ion could be performed in the microreactor using a mixture of water and ethanol, thus well defining the actual residence time for the addition step, the resulting iminium product had to be hydrolyzed by sodium hydroxide in water and ethanol in the collection vials due to repetitive clogging of the outlet of the microreactor. Experiments were performed in random order, and the collected samples were analyzed using HPLC (Figure 5). Full conversion was observed with a reaction time of 180 s, a temperature of 60 °C, and a molar ratio of 1.5, which we considered optimal conditions. It may be clear from the model, however, that various other sets of optimal parameters can also be selected, depending on the demands one has to satisfy.

Now being able to reach a full conversion, different solvents were investigated to reduce the use of DMF. The results are presented in Table 1, showing that there is an evident

Table 1. Solvent effect

entry	solvent	yield (%)[a]
1	DMF	>99
2	1,2-dichloroethane	92
3	acetonitrile	98
4	THF	79
5	EtOAc	74
6	diglyme	69

[a]Conditions: t_r = 180 s, T = 60 °C, MR = 1.5

difference in the conversion to 2-formylpyrrole (**6**) in different solvents. The results indicate comparable reaction rates for polar solvents such as DMF (entry 1) and acetonitrile (entry 3) compared to the less polar THF, EtOAc, and diglyme (entries 4−6). Even though the reaction rate is slightly lower in the latter solvents, they clearly show additional value by being less toxic.

Scaling up of the Vilsmeier−Haack formylation in batch reactors generally poses thermal runaway threats due to the highly exothermic formation of the reactive species. In flow chemistry, scaling out is a one-to-one process in most cases, eliminating the need for active cooling. Using optimal conditions obtained from the optimization data, a preparative synthesis of 2-formylpyrrole (**6**) resulted in the continuous production at a 6.0 g/h rate (see: Experimental Section), using the Uniqsis FlowSyn (FCUQ-1020) with a Uniqsis FlowSyn (FCUQ-1020) equipped with a glass microreactor (0.65 mL) containing folding flow type mixing units and a 2.4 mL stainless steel coil reactor with an internal diameter of 1 mm. The Vilsmeier−Haack reagent was formed in the glass microreactor with a reaction time of 97.5 s, and the outflow was directly pumped into the coil for the oxidation of the pyrrole to

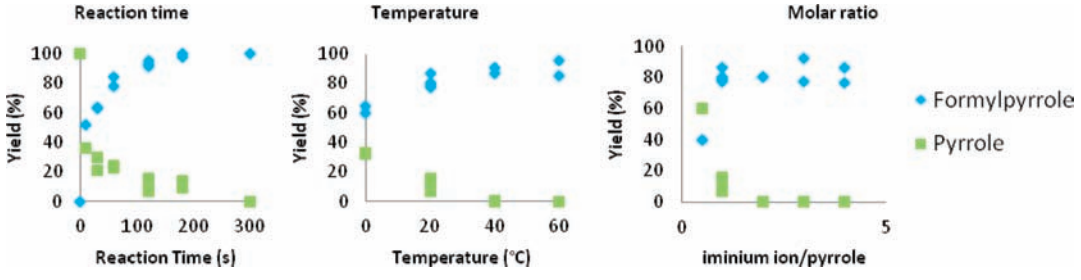

Figure 5. Univariate screening of reaction parameters. Fixed values were a reaction time of 180 s, a temperature of 20 °C, and a molar ratio of 1.5.

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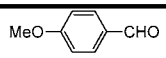
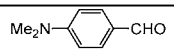
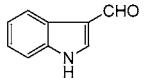
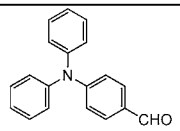
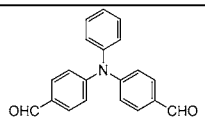
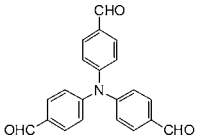
Table 2. Preparative-scale experiments

Entry	Substrate	Product		Isolated yield (%)[a]
1	**6**		**7**	<5
2	**8**		**9**	61
3	**10**		**11**	62
4	**12**		**13**	81
5	**13**		**14**	47 (**13**)[c] 53 (**14**)[c]
6	**14**		**15**	<5[b]

[a]Conditions: t_r = 180 s, T = 60 °C, MR = 1.5. [b]Conditions: t_r = 180 s, T = 100 °C, MR = 1.5. [c]Conditions: t_r = 360 s, T = 100 °C, MR = 1.5.

proceed. Quenching of the reaction was not required now since the reaction was driven to full completion. The intermediate iminium species was therefore continuously hydrolyzed in a solution of NaOH (0.27 M) for 60 min and subsequently extracted with Et_2O to yield 5.98 g (98%). The yield obtained was similar to that found in the optimization using a reactor with an internal volume of 92 μL.

On the basis of the optimal conditions obtained with pyrrole, a range of different substrates were screened (Table 2). The conversion of the reactions was determined by HPLC and confirmed by high resolution mass spectrometry. Isolated yields are depicted in Table 2. It was concluded that amine-substituted arenes (entries 2−5) are highly reactive towards Vilsmeier−Haack formylation, all showing high or complete conversion within 180 s. Di- and triformylation of triphenylamine **12** proved to be less effective, resulting in extended reaction times at elevated temperatures to reach full conversion. Anisole (**6**, entry 1) appeared much less reactive than its amine substituted derivative **8** since only trace amounts of product were observed.

3. EXPERIMENTAL SECTION

Reaction Optimization. A FutureChemistry FlowScreen (C-300) was used to perform the reaction parameter screening. Four glass syringes with an internal volume of either 1 or 5 mL were used, as indicated in Figure 1. Pumps 1 and 2 were loaded with $POCl_3$ and DMF, respectively, for the formation of the Vilsmeier−Haack reagent. Pump 3 contained a solution of pyrrole (**6**, 1.85 mL, 26.7 mmol) and toluene (1.91 mL, internal standard) in DMF with a total volume of 10 mL. In order to quench the reaction at the end of the microreactor, ensuring well-defined reaction times, pump 4 contained a solution of EtOH/H_2O (5 mL, 1:1, v/v). The intermediate iminium ion **3** was hydrolyzed in NaOH/EtOH/H_2O (1 mL, 0.27 M, 1:1, v/v) to ensure solubility of the internal standard.

Scale-Up Reaction. A scale-up experiment was performed in a Uniqsis FlowSyn (FCUQ-1020) equipped with a glass microreactor (0.65 mL) containing folding flow type mixing units and a 2.4 mL stainless steel coil reactor with an internal diameter of 1 mm. With flow A of 0.1 mL/min and flow B of 0.3 mL/min, a reaction time for formation of the VH reagent of 97.5 s was obtained. It was reacted in the coil with a solution of pyrrole (**4**, 7.40 mL, 106.8 mmol) in DMF (32.60 mL). With a total flow rate of 0.8 mL/min, a reaction time of 180 s was obtained. After a stabilization time of 10 min, the product was collected for 60 min. In contrast to the optimization, no inline quench was used, because the reaction was driven to full conversion now. Instead, the outflow of the reactor was directly collected in a stirred solution of NaOH/H_2O (400 mL, 0.27 M). The product collected was extracted with Et_2O (3 × 200 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo (700 mbar, 40 °C) to yield 5.98 g of 2-formylpyrrole (**6**, 98%) as a viscous oil which solidified upon standing at −18 °C for 16 h. Purity (93%) was based on NMR measurements.[27]

UV Analysis. To a UV vial containing acetonitrile (1 mL) was added $POCl_3$ (5 μL, 55 μmol) and DMF (5 μL, 65 μmol). The vial was stoppered, quickly shaken, and immediately inserted into a UV/vis spectrometer. The spectrometer measured the UV spectrum with 15 s intervals. In between the measurements, the vial was taken out of the spectrometer and shaken to homogenize the sample and promote the reaction.

IR Analysis. A FutureChemistry FlowStart Evo (B-400) was placed in line with the FlowIR (Mettler Toledo) to analyze the formation of the VH reagent. Two glass syringes with an

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internal volume of 5 mL were used, and pumps 1 and 2 were loaded with $POCl_3$ and DMF. A reactor with an internal volume of 100 μL was connected to the FlowIR with a total system volume of 120 μL, including the flow cell of the FlowIR. Flows were fixed to corresponding reaction times, and IR spectra were recorded continuously.

HPLC Analysis. Atline HPLC-analysis was performed, and samples were loaded into the injector of a Shimadzu HPLC system (Adsorbosphere C18 column (length: 100 mm, ID: 4.6 mm)) with a flow rate of 1.0 mL/min; acetonitrile/water: initial (40/60); 4.0 min (40/60); 12.5 min (90/10); 13.0 (40/60); 17.5 (40/60), using a UV detector with analysis channels at 210 and 254 nm. Accurate flow rates of the substrate in the optimization experiments were calculated using toluene as an internal standard and determined with our recently developed flow marker methodology.[28]

4. CONCLUSION

It has been demonstrated that the Vilsmeier−Haack formylation can be readily performed in a continuous flow microreactor system. A full optimization study was performed involving reaction time (t_r), temperature (T) and molar ratio (MR) as process parameters. Optimal conditions were obtained at a reaction time of 180 s at 60 °C with a molar ration of 1.5 and DMF as a solvent. Other less toxic solvents also showed remarkably high conversions within 180 s. Under the optimized conditions, scale-up of the reaction has been successfully realized with a continuous production of 2-formylpyrrole of 5.98 g/h. The newly developed process was also shown to be more widely applicable by the successful formylation of several amine-substituted arenes.

■ ASSOCIATED CONTENT

Supporting Information

More detailed information on GC retention times and reaction data. This material is available free of charge via the Internet at http://pubs.acs.org.

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