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A Vilsmeier Chloroformylation by Continuous Flow Chemistry

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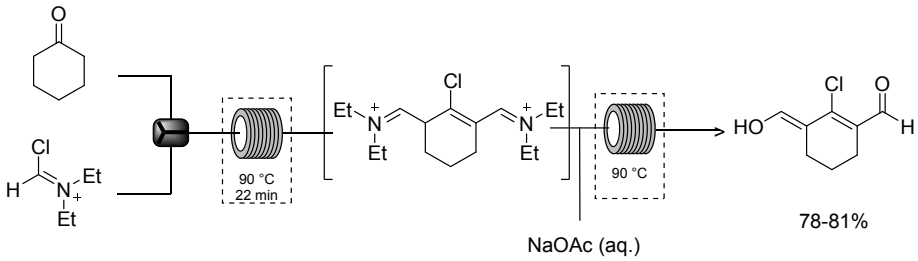
TOC – Graphical abstract



ABSTRACT. Chloroformylation reactions are versatile reactions that allow the introduction of a chlorine atom and an aldehyde group in enolizable ketones, employing the well-known Vilsmeier reagent. However, the use of this unstable reagent is usually associated with hazards, especially when it is used on an industrial scale. The present article describes the preparation and use of the Vilsmeier reagent under continuous flow conditions for the preparation of an important intermediate in the synthesis of cyanine dyes. In addition, the traditionally used DMF has been substituted with more desirable formamides, together with the removal of the halogenated solvent usually employed in the reaction. In consequence, the optimized conditions allow the continuous production of the target compound in 79-81 % isolated yield in a more environmentally friendly, fast and secure manner.

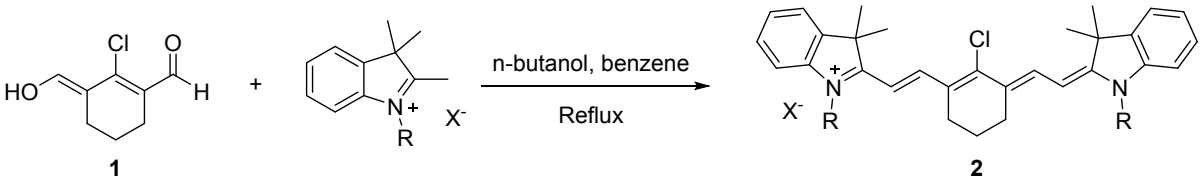
KEYWORDS. Vilsmeier reagent, Chloroformylation, Flow Chemistry, Cyanine dyes, 2-Chloro-1-formyl-3-(hydroxymethylene)cyclohex-1-ene.

INTRODUCTION.

The Vilsmeier-Haack reaction was reported in 1927 for the formylation of electron-rich arenes.[1] The formylation reagent, known as Vilsmeier or Vilsmeier-Haack reagent, is formed *in situ* from DMF and a chlorinating agent, with $POCl_3$ being the most common. The Vilsmeier reagent has been widely used for formylation,[2] chlorination,[3] chloroformylation,[4] cyclization,[5] among other reactions.[6] Despite the convenience of the Vilsmeier reagent, the scale-up of the reaction is troublesome due to its instability. This is usually controlled by dosing the reagents over a long time, by the dilution of the reaction mixture and a good control over the reaction temperature. Previous studies reported the thermal hazards associated with the Vilsmeier reaction, that in extreme cases can lead to an explosion due to gas evolution during the exothermic decomposition of the Vilsmeier reagent.[7]

Continuous flow chemistry allows a precise control over the reaction parameters, and is becoming more and more utilized both in academia and industry.[8] The main benefits of this technology are the better mixing, the more efficient heat transfer and the easy scale-up. Due to the highly efficient heat transfer, exothermic reactions are better controlled and the technology offers opportunities for reactions that present very reactive or unstable intermediates. Together with that, the amount of dangerous material present in the reactor is limited in flow, making the flow process far more safer than the hazardous reactions performed in batch, such as the Vilsmeier reaction. In fact, because of safety reasons, the Vilsmeier reagent has been previously used under continuous flow conditions for the formylation of activated arenes,[9] the synthesis of *β*-chloro enals,[10] chlorinations,[11] and the synthesis of Vildagliptin.[12]

2-Chloro-1-formyl-3-(hydroxymethylene)cyclohex-1-ene (**1**) is an important intermediate for the synthesis of heptamethine cyanine dyes (**2**).[13] This kind of cyanine dye derivatives are known for their properties as near infrared fluorescence probes,[14] studied for applications as chemosensors,[15] *in vivo* imaging,[16] tumor detection,[17] or photothermal therapy of cancer,[18] among others. Compound **1** can be easily obtained by Vilsmeier chloroformylation from cyclohexanone (CH) as described in references mentioned above. The conjugated aldehyde and enol groups present in the molecule allow an easy symmetric derivatization (Scheme 1), while the Cl substituent allows further functionalization.

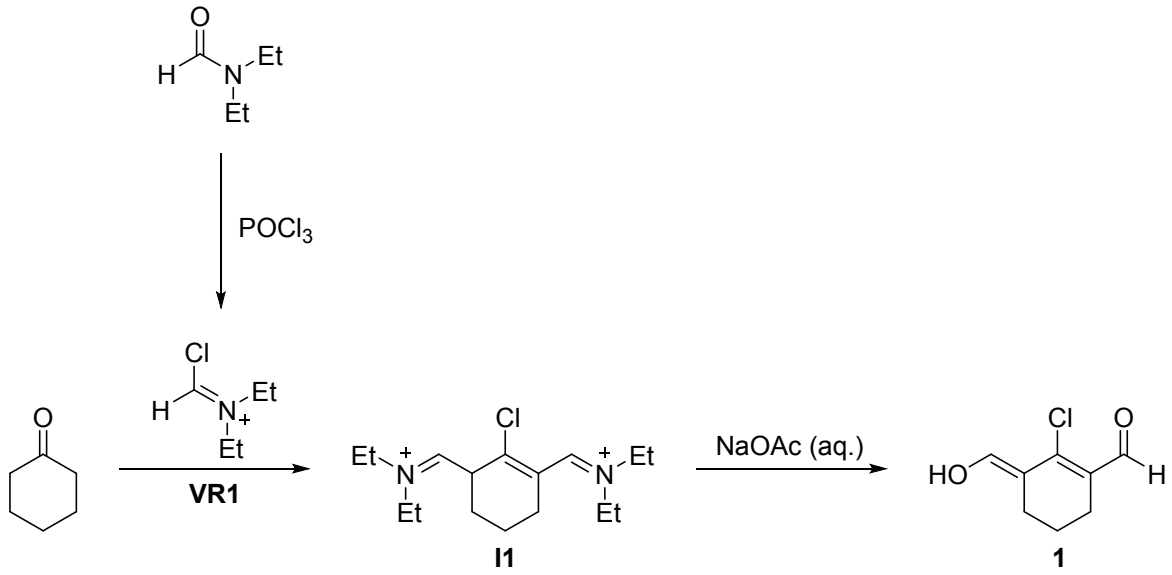


Scheme 1. General synthesis of cyanine dyes from compound 1.[19]

RESULTS AND DISCUSSION.

DMF is a substance of very high concern (SVHC) included in the candidate list for authorization of the European Chemical Agency (ECHA) and has a severe and well described potential safety hazard.[20] As DMF can be replaced by DEF (*N*,*N*-diethyl formamide), which is more desirable from an industrial point of view, the Vilsmeier reagent was prepared from DEF and $POCl_3$. At the moment, diethyl formamide and N-formylmorpholine are still more expensive than DMF, however N-formylmorpholine is considered in different areas as a green alternative for DMF most probably leading to an increased use in the future.[21, 22]

For the synthesis of the target molecule (compound **1**), cyclohexanone (CH) was reacted with the Vilsmeier reagent (**VR1**), prepared *in situ* at r.t., to afford the intermediate **I1**, which after hydrolysis with NaOAc (aq.), yields the target compound **1** (Scheme 2).



Scheme 2. Synthetic route for the synthesis of compound **1**.

Initially, the conditions for the synthesis of the Vilsmeier reagent were optimized under continuous flow conditions. The conversion was determined by ^{31}P-NMR, always within 5

minutes after the sample collection. After 2.5 minutes of residence time, full conversion was obtained when 2 equivalents of DEF were employed (Table 1, entry 3). With less equivalents of DEF (Table 1, entry 1) or an excess of $POCl_3$ (Table 1, entry 2), no full conversion was achieved with the same residence time. Keeping the same optimized ratio between both reagents, full conversion was also achieved at higher residence times, showing no decomposition of the Vilsmeier reagent on ^{13}C-NMR after 10 minutes at room temperature (Table 1, entries 4 and 5). Thus, the Vilsmeier reagent can be prepared extremely fast at room temperature under continuous flow conditions and did not show any decomposition for at least 10 minutes in the flow reactor, affording a viscous homogeneous pale-yellow oil output stream.

Table 1. Optimization of continuous flow synthesis of Vilsmeier reagent from DEF/$POCl_3$.

Entry	$POCl_3$ (equiv.)	DEF (equiv.)	T (°C)	t_r (min.)	Conv.[a] of $POCl_3$ (%)
1	1	1.5	r.t.	2.5	96
2	1.1	1	r.t.	2.5	75
3	1	2	r.t.	2.5	100
4	1	2	r.t.	5	100
5	1	2	r.t.	10	100

[a]: Determined by ^{31}P-NMR analysis within 5 minutes after sample collection

With the conditions for the formation of the Vilsmeier reagent in hand, we moved forward to a full reaction continuous flow set-up. Three sequentially coupled tubular PTFE reactors were used. In the first reactor (R1, Figure 1), the Vilsmeier reagent was generated. In the second reactor (R2, Figure 1), the Vilsmeier reagent was reacted with the substrate (cyclohexanone). In

the last reactor (R3, Figure 1), the reaction mixture was quenched with aqueous sodium acetate. Two different temperatures were used during the reaction. For the formation of the Vilsmeier reagent, room temperature was used, while for the other two reactors (R2 and R3, Figure 1) the same temperature was used, with the advantage of using just one heating bath. After hydrolysis, the reaction mixture was collected and stirred in an Erlenmeyer flask which was cooled by an ice bath for the precipitation of the target compound. After stirring for 30 minutes at 0 °C, the product was filtered off and washed with cold water to obtain the isolated compound as a yellow solid.

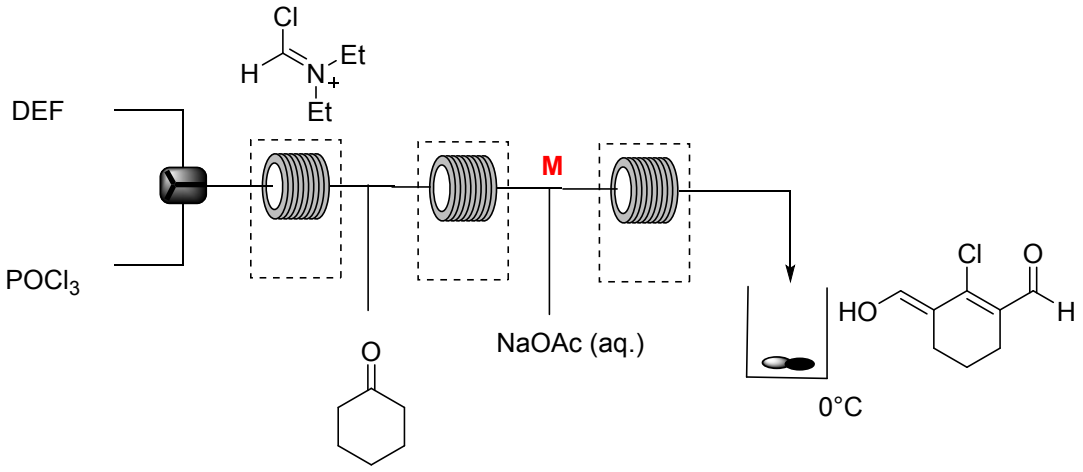


Figure 1. Full reaction set-up for continuous flow synthesis of compound **1**. Mixer position M is indicated in red.

For the first experiment (Table 2, entry 1), the conditions of Table 1, entry 5 were used to generate the Vilsmeier reagent in reactor R1. Cyclohexanone was then introduced in the Vilsmeier reagent stream via a T-junction. Since the cyclohexanone core needs functionalization at three different positions, three equivalents of Vilsmeier reagent were required. Initially, a temperature of 80 °C and a residence time of 22 minutes were chosen for reactor R2. The hydrolysis of the intermediate **I1** is a fast reaction, and thus a short residence time of 5 minutes

was chosen for reactor R3. This resulted in a product yield of 66%. The moderate yield was mainly due to incomplete conversion in reactor R2. Besides that, it was observed that very tiny droplets of an orange oil crashed out of the quenched reaction stream in reactor R3, consisting of incompletely converted cyclohexanone next to some other unidentified side products. Therefore, the effect of the mixing during the aqueous quenching was evaluated because the highly viscous stream coming from reactor R2 and the aqueous sodium acetate solution behave as two different phases, which leads to inefficient mixing. Thus, the T-junction at mixer position M (Figure 1) was replaced by a 5-port manifold in T-configuration with a 180° contact angle and the 2 other inlet ports closed (Table 2, entry 2). This configuration results in a larger mixing chamber compared to the T-junction, allowing for more turbulence. Next to that, an Uniqsys Flowsyn glass static mixer chip with an internal volume of 2 mL was evaluated at mixing position M (Table 2, entry 3). These different mixers had almost no influence on the product yield, and values of 66-68% were observed. This small change in product yield did not justify the use of the expensive and fragile Uniqsys chip in further experiments. In a next run, the residence time in reactor R2 was increased to 35 minutes, resulting in an increased product yield of 74% (Table 2, entry 4). However, a further increase of reactor residence time was not desired. Thus, the temperature of reactors R2 and R3 was increased to 90 °C (Table 2, Entries 5-7). A residence time of 12 minutes in reactor R2 gave 74% yield (Table 2, entry 5), and this value increased further to 81% for a residence time of 22 minutes (Table 2, entry 6). At this point, the continuous flow process had already matched the product yield of the batch production process. An increase of the residence time of reactor R2 to 35 minutes did not improve the product yield any further (Table 2, entry 7). A possible reason for the stagnating product yield could be that the reaction stream in reactor R2 became so viscous that it gave rise to mass transfer problems. The addition

of a higher loading of DEF could possibly reduce the viscosity of the product stream in reactor R2, but an increase in solvent use was not desired because it leads to a decreased product output. The temperature was increased to 95 °C (Table 2, entry 8), but this did not result in a better product yield compared to Table 2, entry 5. Also, a slight color change of the reaction stream in reactor R2 was observed at this temperature, which could be an indication of an undesired side reaction or degradation process. The goal of the next experiments was to minimize the total residence time of the reaction. The residence time for the Vilsmeier reaction in reactor R1 could be reduced to 5 minutes, while a residence time in reactor R2 of at least 22 minutes proved to be necessary (Table 2, Entries 9-11). In a final experiment, the amount of sodium acetate was lowered to three equivalents and this gave 76% product yield. The highest yield obtained was 81% (Table 2, entry 6), affording 3.075 g of product in 26 minutes.

Table 2. Optimization for the continuous flow synthesis of compound **1**, using DEF and $POCl_3$.

Entry	$POCl_3$ (eq.)	DEF (eq.)	CH (eq.)	NaOAc (eq.)	t_{r1} (min.)	T_1 (°C)	t_{r2} (min.)	t_{r3} (min.)	$T_{2,3}$ (°C)	Mixer (M)	Yield (%)
1	3	6	1	4	10	r.t.	22	5	80	A	66
2	3	6	1	4	10	r.t.	22	5	80	B	66
3	3	6	1	4	10	r.t.	22	6	80	C	68
4	3	6	1	4	10	r.t.	35	5	80	B	74
5	3	6	1	4	10	r.t.	12	5	90	B	74
6	3	6	1	4	10	r.t.	22	5	90	B	81
7	3	6	1	4	10	r.t.	35	5	90	B	79
8	3	6	1	4	11	r.t.	12	5	95	B	74
9	3	6	1	4	5	r.t.	15	5	90	A	71
10	3	6	1	4	5	r.t.	19	5	90	A	75
11	3	6	1	4	5	r.t.	22.5	5	90	A	78
12	3	6	1	3	5	r.t.	22.5	5	90	A	76

A: T-junction. B: 5-port manifold in T-configuration (180° contact angle, the 2 other side ports were closed). C: Uniqsys Flowsyn static mixer chip (2 mL internal volume).

NFM (*N*-Formylmorpholine) is even more acceptable than DEF from an environmental and industrial point of view because of the lower toxicity and the higher flash point.[23] Thus, the Vilsmeier reagent formation was evaluated with NFM instead of DEF. The same conditions previously optimized for DEF were employed, obtaining full conversion of $POCl_3$ after a residence time of 5 minutes at room temperature under continuous flow conditions.

However, when the full reaction set-up (Figure 1, with NFM instead of DEF) was tested using the same previously optimized conditions, problems with high pressure (> 50 bar) were observed during the reaction, giving rise to equipment and safety issues. The high pressure could be due to the higher viscosity of the reaction mixture with NFM. In order to solve that problem, the equivalents of NFM were increased from 6 to 8, as NMF is used as solvent for the reaction. Another problem that appeared during the switch from DEF to NFM was the tendency of the final product to crash out in reactor R3. Therefore, the amount of sodium acetate was increased to 8 equivalents and the residence time in reactor R3 was simultaneously decreased to 3 minutes by rising the flow rate of the sodium acetate solution (Table 3, entry 1). This afforded the product in 79% yield. Decreasing the flow rate of the sodium acetate solution to 6 equivalents gave rise to small amounts of product crashing out in reactor R3. Although the product yield was 78%, these reaction conditions were not preferred. An increase of the equivalents of $POCl_3$ did not lead to an improvement of the yield, despite the fact that an excess of Vilsmeier reagent would be available in the reaction medium (Table 3, entry 3). The highest yield obtained was 79 % (Table 3, entry 1), affording 2.643 grams of product in 25 minutes.

Table 3. Optimization for the continuous flow synthesis of compound **1** from NFM and $POCl_3$.

Entry	$POCl_3$ (eq.)	NFM (eq.)	CH (eq.)	NaOAc (eq.)	t_{r1} (min.)	T_1 (°C)	t_{r2} (min.)	t_{r3} (min.)	$T_{2,3}$ (°C)	Mixer (M)	Yield (%)
1	3	8	1	8	9.4	25	21	3	90	B	79
2	3	8	1	6	9.4	25	21	3	90	B	78
3	3.3	8	1	6	5	25	17	3	90	B	76

B: 5-port manifold in T-configuration (180° contact angle, the 2 other side ports were closed).

A batch reaction was performed on a 5 mmol scale for the synthesis of compound **1**, using the same conditions as in flow, obtaining 80 % isolated yield after 3 hours of reaction. The same yield can be obtained using batch or continuous flow synthesis for a small-scale preparation of compound **1**. However, for a bigger scale, the flow process will be the preferred choice due to the superior heat and mass transfer and inherent safety.

CONCLUSION.

In summary, the synthesis of 2-chloro-1-formyl-3-(hydroxymethylene)cyclohex-1-ene (**1**), an important industrially produced intermediate, was developed in continuous flow using a Vilsmeier reagent that was prepared from DEF or NFM, which are much more environmentally friendly than DMF. Under the developed conditions, the use of solvent, usually CH_2Cl_2, is not necessary thanks to the highly efficient heat transfer under flow conditions. In addition, the rate of the reaction is much higher under flow conditions, obtaining complete conversion after 21-22 minutes of reaction between the Vilsmeier reagent and the cyclohexanone instead of 2-3 hours of reaction that can be found in the literature for the synthesis of compound **1**. Overall, the conditions developed afford a 79-81% isolated yield using more environmentally friendly formyl amides, using no halogenated solvents in a faster reaction and under much safer reaction conditions.

EXPERIMENTAL SECTION.

General:

Commercially available starting materials (Sigma-Aldrich, Fisher Scientific, TCI Europe) and solvents were used without further purification. NMR spectra were recorded on a Bruker Avance

III (400 MHz for ^{1}H-NMR, 101 MHz for ^{13}C-NMR and 162 MHz for ^{31}P-NMR), equipped with a ^{1}H/BB z-gradient probe (BBO, 5 mm). DMSO-d_6 and $CDCl_3$ were used as solvents and TMS as internal chemical shift standard in the $CDCl_3$. LC-MS analysis was performed with Agilent 1200 Series HPLC equipped with a Supelco Ascentis Express C18 column (3 cm x 4.6 mm, 2.7 µm fused-core particles, 90 Å), Phenomenex Guard column (SecurityGuard Standard) and a UV-DAD detector. MS spectra were obtained with an Agilent 1100 Series MS with electrospray ionisation (70 eV) with a single quadrupole detector. IR spectra were obtained from neat samples with a Quest ATR accessory with diamond crystal puck using a Shimadzu IRAFFINITY-1S Fourier Transform Infrared Spectrophotometer. HRMS was recorded using a Thermo Fisher QExtractive MS, with loop injection in 350 µL/min. MeOH+0.1%FA/H_2O+0.1%FA 50/50 and ESI positive mode (3.5 kV of Spray Voltage) with a mass resolution of 70000 (FWHM).

Flow synthesis:

The formation of the Vilsmeier reagent (Table 1) was studied in a simple flow reaction set-up, consisting of two Chemyx Fusion 100 syringe pumps, two Hamilton 81610 glass syringes, Luer lock connectors (P-628, IDEX Health & Science, USA) and PTFE tubing (I.D. 1.0 mm, O.D. 1/16", S1810-12, BOLA, Germany). Tubing ends were fitted with PEEK nuts (XP-230x, IDEX Health & Science, USA) and ETFE ferrules (P200x, IDEX Health & Science, USA). Mixing of the two reagent streams was accomplished with an ETFE T-junction (P-632, IDEX Health & Science, USA). The reactor was made of a coil of PTFE tubing (S1810-12, BOLA, Germany) with a coil diameter of 10 cm and internal volume of 4 mL. Samples were collected at the outlet after an equilibration period of three times the theoretical residence time.

The formation of compound **1** was performed in a flow reaction set-up as depicted in Figure 1. $POCl_3$ and DEF/NFM were pumped with two Reaxus 6010R Hastelloy reciprocating pumps (Teledyne Isco, USA). Cyclohexanone was pumped with a WADose Lite HP reciprocating pump (Flusys, Germany). Aqueous sodium acetate was pumped with a Vapourtec peristaltic V-3 pump (easy-MedChem, Vapourtec, UK). The pumps were connected to PTFE tubing (I.D. 1.0 mm, O.D. 1/16", S1810-12, BOLA, Germany) with PEEK nuts (XP-230x, IDEX Health & Science, USA) and ETFE ferrules (P200x, IDEX Health & Science, USA). Mixing of the POCl3 and DEF/NFM reagent streams was accomplished with an ETFE T-junction (P-632, IDEX Health & Science, USA). The reactor (R1) was made of a coil of PTFE tubing (S1810-12, BOLA, Germany) with a coil diameter of 10 cm. Mixing of the Vilsmeier reagent stream from reactor R1 and the cyclohexanone reagent stream was accomplished with an ETFE T-junction (P-632, IDEX Health & Science, USA). Reactor R2 was made of a coil of PTFE tubing (I.D. 2.0 mm, O.D. 3 mm, S1810-30, BOLA, Germany) with a coil diameter of 10 cm. This tubing was fitted with PEEK nuts (P-331x, IDEX Health & Science, USA) and PEEK ferrules (P-350x, IDEX Health & Science, USA). The reactor R2 was placed in a thermostatic oil bath equipped with a stirring bar (800 rpm). Mixing of the product stream from reactor R2 and the aqueous sodium acetate reagent stream was accomplished with an ETFE T-junction (P-633, IDEX Health & Science, USA) or a PEEK 5-port manifold in T-configuration (180° contact angle, the 2 other side ports were closed) (P-155, IDEX Health & Science, USA) or a Uniqsys Flowsyn glass static mixer chip with internal volume of 2 mL (Uniqsys, UK). This mixing unit was also placed in the thermostatic oil bath. Reactor R3 was made of a coil of PTFE tubing (I.D. 2.4 mm, O.D. 1/8", S1810-33, BOLA, Germany) with a coil diameter of 10 cm and placed in the thermostatic oil bath. This tubing was fitted with PEEK nuts (XP-330x, IDEX Health & Science, USA) and

ETFE ferrules (XP-300x, IDEX Health & Science, USA).The outlet of reactor R3 (the part of the tubing coming out of the thermostatic oil bath) was insulated with aluminium foil to avoid a temperature drop and to prevent undesired crystallization of compound **1** inside the tubing. The sample was collected after an equilibration period of three times the total theoretical residence time of the system. The sample was collected in an Erlenmeyer flask equipped with a stirring bar and cooled with an ice bath. After stirring for 30 minutes at 0 °C, the product was collected by filtration over a glass sintered filter and rinsed with ice-cold water. The filtered solids were transferred to a glass round-bottomed flask and dried under high vacuum to afford compound **1** as a yellow powder.

Batch synthesis:

In a 50 mL round-bottomed flask, equipped with a stirring bar, in a water bath at room temperature and under nitrogen atmosphere, NFM (8 equiv., 40 mmol, 4.0 mL) was introduced. Then, $POCl_3$ (3 equiv., 15 mmol, 1.4 mL) was added to the NFM, drop by drop, and the viscous reaction mixture was stirred at room temperature for 30 minutes, changing from colourless to yellow. Then, cyclohexanone (5 mmol, 0.4945 g) was added to the yellow mixture at room temperature (water bath) and the mixture was heated at 80 °C on a preheated oil bath. During the heating of the reaction mixture, it changed from yellow to orange to red, and some evaporation-crystallization was observed on the top of the flask (white and yellow). After 3 hours of reaction, the mixture was cooled down to r.t., and 40 mL of NaOAc (2M) was added for the hydrolysis. The very viscous dark red reaction mixture did not mix well with the aqueous solution, so it was warmed to 30 °C, and stirred with a spatula until the stirring bar was free. Then, it was stirred at r.t. until no viscous material was present, about 20 minutes, to obtain a yellow solid in an orange

aqueous solution. After storing of the solution overnight in the fridge, the yellow solid was filtered off, washed with cold water and dried under high vacuum to afford a yellow powder (0.6921 g, 80 %).

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

Representative flow synthesis and characterization of compound **1**, and ^{1}H-NMR, ^{13}C-NMR, IR and HRMS data for compound **1**. (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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Notes

Any additional relevant notes should be placed here.

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ABBREVIATIONS

DMF, *N*,*N*-diethyl formamide; DEF, *N*,*N*-diethyl formamide: NFM, *N*-formylmorpholine; CH, cyclohexanone; SVHC, substance of very high concern; ECHA; European Chemical Agency.

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