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Continuous-Flow Preparation and Use of β-Chloro Enals Using the Vilsmeier Reagent

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Supporting Information

ABSTRACT: The Vilsmeier reagent is used in the preparation of a wide variety of heterocycles, such as pyrazoles, *via* formation of β-chloroacrolein intermediates. However, use of this extremely reactive reagent on large scale requires special precautions to avoid potentially dangerous exotherms. This article describes the safe preparation at room temperature of the Vilsmeier reagent under flow conditions for the formation of β-chloroacroleins and 3-formylchromones, as well as the use of these in multistep, continuous flow processes for the syntheses of β-acrylonitriles and polysubstituted pyrazoles.

INTRODUCTION

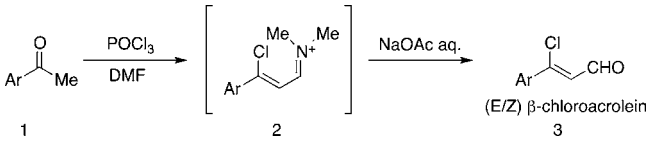
Since Anton Vilsmeier and Albrecht Haack first reported it in 1927,[1] the Vilsmeier reagent (VR) has been widely used for the formylation of activated arene compounds. Beyond this initially reported use, the VR has also been employed for the preparation of β-chloroacroleins and β-chloroacrylonitriles from acetophenones,[2] which can in turn provide access to a variety of heterocycles, such as pyrimidines,[3,4] isothiazoles,[5] oxazoles,[6] isoxazoles,[4] pyrazole,[4] aminopyrazoles,[7] furan,[8] thiophenes,[9] and pyrroles.[10] Despite the fact that these reactions have been extensively studied over the last century,[11] the industrial use of the Vilsmeier reagent still requires careful handling, due the extreme instability of the chloroiminium ion. In the worst case, this instability can lead to an explosion,[12] although this situation is typically avoided through careful temperature control and/or dilute reaction conditions.

The development of chemical transformations under continuous flow conditions has gained considerable attention over the past decade.[13] This is due, in part, to the benefits associated with continuous processing, such as increased reaction efficiency and waste minimization.[13−15] The use of flow systems can also allow for the safe handling of hazardous and/or highly reactive starting materials and/or intermediates, such as the Vilsmeier reagent. Recently, Rutjes reported the controlled use of the VR for the formylation of electron-rich arenes using microreactors under continuous flow conditions.[16] Herein, we disclose the preparation of the Vilsmeier reagent and its direct application to the synthesis of pyrazole derivatives under flow conditions.

RESULTS AND DISCUSSION

We set out to investigate the formation of β-chloroacroleins starting from acetophenone derivatives and *in situ* generated VR. We chose to employ DMF and phosphorus oxychloride as precursors for the preparation of the VR (Scheme 1),[11] a typical combination that also minimizes the formation of *N*,*N*-dimethylcarbamoyl chloride (DMCC), a potential carcinogen.[17] Upon subsequent introduction of acetophenone and heating, the chloroiminium salt (**2**) is formed, which is hydrolyzed to the corresponding β-chloroacrolein (**3**) upon workup.

Scheme 1. Preparation of β-chloroacroleins using $POCl_3$ and DMF as VR precursors



With this strategy in mind, we designed the continuous-flow system depicted in Figure 1. Neat phosphorus oxychloride and DMF were merged using a Tee-mixer (0.04 in. ID) and introduced into the first reactor (PFA tubing-0.04 in. ID) at room temperature for 1.1−4.4 min to form the VR. A stream of acetophenone in DMF was then mixed with the VR and this combination is flowed into the second reactor (PFA tubing-0.04 in. ID), which was submerged in an oil bath. The temperature and the residence time were adjusted depending on the stability and reactivity of the corresponding

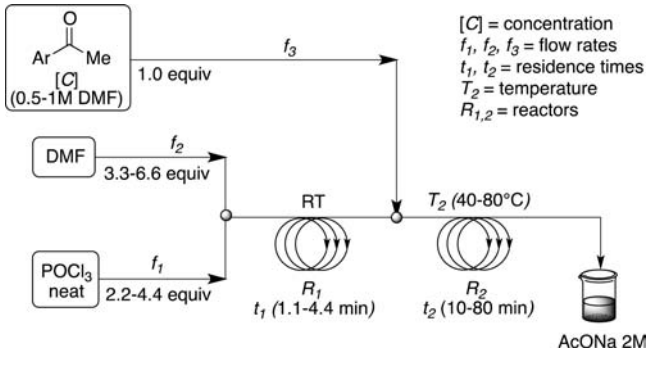


Figure 1. Setup for the preparation of β-chloroacroleins under flow conditions.

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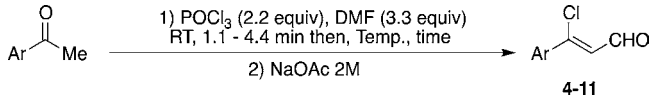
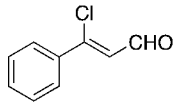
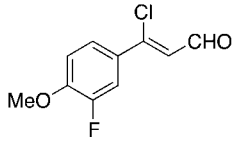
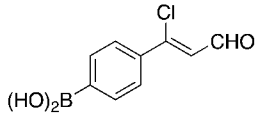
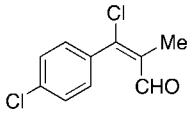
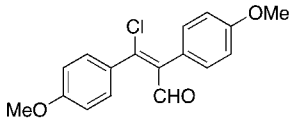
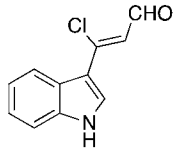
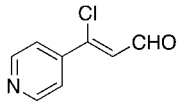
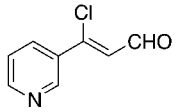
Table 1. Substrate scope for the preparation of β-chloroacroleins



4-11

Entry	T	Res. Time	Product		E/Z	Yield (%)[b]
1	80 °C	20 min		**4**	10/90	92
2	80 °C	20 min		**5**	0/100	70
3	80 °C	30 min		**6**	0/100	89[a]
4	80 °C	20 min		**7**	80/20	98
5	80 °C	48 min		**8**	80/20	90
6	40 °C	10 min		**9**	5/95	43
7	60 °C	60 min		**10**	0/100	27
8	60 °C	80 min		**11**	0/100	26

[a]Conditions: 4.4 equiv $POCl_3$, 6.6 equiv DMF. [b]Yields are of isolated products collected after equilibration of the system (average of two or more runs).

chloroiminium ion (40−80 °C, 10−80 min). The crude reaction mixture was then added to a flask containing aqueous NaOAc solution (2 M), after which time the β-chloroacroleins were isolated, in some cases as *E*/*Z*-mixtures.

Using the setup depicted in Figure 1, various substituted acetophenones were efficiently converted to the corresponding β-chloroacroleins or 3-formylchromones (Table 1). Notably, the transformation was tolerant of a boronic acid moiety and product **6** was obtained in 89% yield. Tetrasubstituted alkenes **7** and **8** could also be obtained in good yields (Table 1, entries 4−5), though in the case of compound **8** a residence time of 48 min was necessary in order for the reaction to reach full conversion from 4′-methoxy-2-(4-methoxyphenyl)-acetophenone. This methodology was then applied to several acetyl heterocycles (Table 1, entries 6−8), and we found that β-chloroacroleins **9**−**11** could be obtained, albeit in modest

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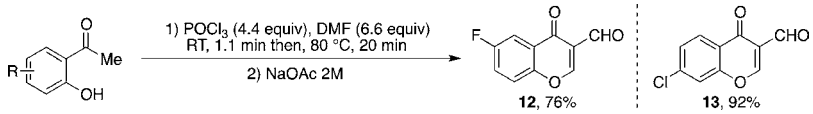
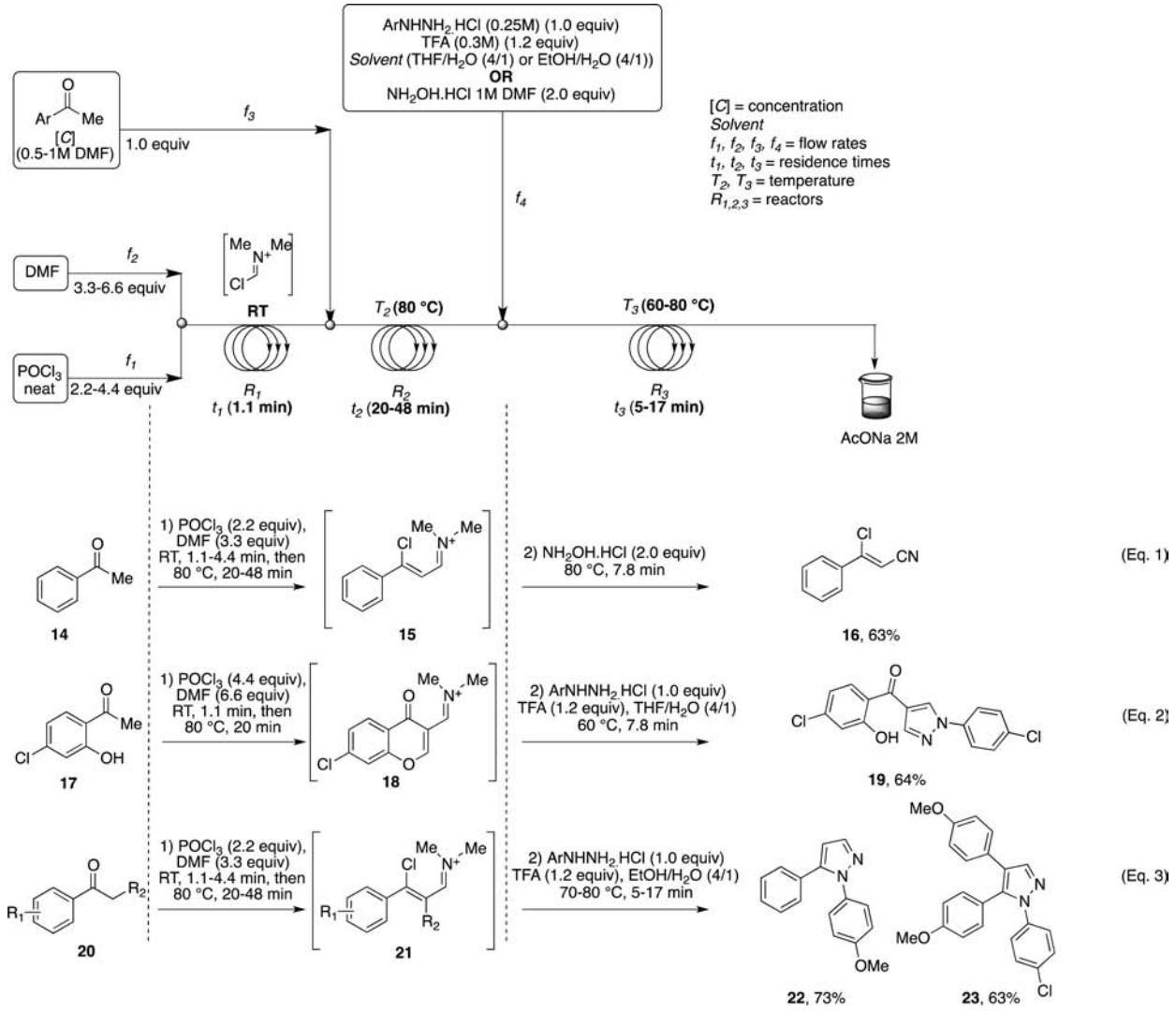
Scheme 2. Reaction sequence for the preparation of 3-formylchromones



Scheme 3. Continuous flow synthesis of β-chloroacrylonitriles and pyrazole derivatives



yields. The inefficiency of the reaction sequence with these heterocyclic compounds as substrates is presumably a consequence of the low stability of the corresponding iminium salts, which decompose prior to aqueous workup. Additional examples of reactions of heterocyclic substrates are provided in the Supporting Information (SI). Finally, we found that substituted 3-formylchromones could be obtained in excellent yields from corresponding 2′-hydroxy acetophenones (Scheme 2).

Next, we sought to use the β-chloroacroleins generated in this process for further transformations under flow conditions. For example, β-chloroacrylonitriles can be formed from β-chloroacroleins *via* treatment with hydroxylamine hydrochloride. As this transformation is also reported to be highly exothermic, it is well-suited for application in a continuous-flow process (Scheme 3, eq 1).[18] Thus, a solution of hydroxylamine hydrochloride in DMF (1 M) was mixed with the crude β-chloroiminium salt, derived from acetophenone, under flow conditions and introduced into a third reactor at 80 °C for 7.8 min. The reaction stream was subsequently collected in a flask containing an aqueous solution of 2 M NaOAc to effect hydrolysis. The desired product, 3-chloro-3-phenylacrylonitrile (**16**), was isolated in 63% yield for the two-step process.

β-Chloroacroleins also serve as key intermediates in the synthesis of a wide range of heterocycles. Thus, we decided to demonstrate the utility of our procedure by preparing functionalized pyrazoles from acetophenones in a multistep process (Scheme 3, eqs 2, 3). Following β-chloroiminium salt formation, the reaction stream was then mixed with a stream containing one equivalent of the hydrochloride salt of an aryl hydrazine hydrochloride and 1.2 equiv of trifluoroacetic acid (TFA) as a THF/water or ethanol/water solution to provide the desired pyrazole product. Starting from 4′-chloro-2′-hydroxyacetophenone (**17**), compound **19** was synthesized in

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64% yield *via* the reaction of the corresponding iminium salt **18** at 60 °C for 7.8 min. Additionally, 1,5-diaryl-substituted pyrazoles **22** and 1,4,5-triaryl-substituted pyrazole **23** were also prepared in good yields from their corresponding ketones (**20**), although in these instances the pyrazole formation required higher temperatures to go to completion (70 and 80 °C, respectively). In both cases, EtOH/water (4:1) was used to deliver the aryl hydrazine and TFA. In the case of **23**, the use of a 5 psi back-pressure regulator was also required.

■ CONCLUSIONS

We have demonstrated the preparation of a variety of β-chloroacrolein derivatives using the Vilsmeier reagent generated in a continuous-flow process. These transformations can be efficiently performed in a safe manner by this continuous process in the generation and reaction of the thermally sensitive Vilsmeier reagent. We have further demonstrated the direct use of the generated β-chloroacroleins, for the synthesis of a β-chloroacrylonitrile and of 1,4-disubstituted, 1,5-diaryl, and 1,4,5-triarylsubstituted pyrazoles under flow conditions. We expect that this technique should be readily adaptable for large-scale work.

■ EXPERIMENTAL SECTION

General Remarks. Flash chromatography, if needed, was performed using a Biotage Isolera 4 instrument with cartridges packed with Silicycle SilicaFlashP60 (230−400 mesh). Continuous flow studies were carried out using Harvard Apparatus syringe pumps PHD-2000 and/or PHD Ultra.

Copies of the ^{1}H and ^{13}C spectra can be found at the end of the SI. All GC analyses were performed on an Agilent 6890 gas chromatograph with an FID detector using a J&W DB-1 column (10 m, 0.1 mm I.D.).

*General Procedure **A** for the Continuous Flow Synthesis of β-Chloroacroleins and 3-Formyl Chromones.* Using the reaction setup as depicted in Figure 1, DMF and $POCl_3$ were loaded into 10 mL plastic syringes and introduced into the first reactor (R_1, t_1) via two separate Harvard Apparatus PHD2000 syringe pumps at two different flow rates, f_1 and f_2. An oven-dried screw-top volumetric flask (25 mL), fitted with a Teflon screw-cap, was charged with the acetophenone substrates (6.25−25 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of three times), and DMF was added *via* syringe to make the solution volume 25 mL. This acetophenone solution was then loaded into a 30 mL plastic syringe and fitted to a third Harvard Apparatus PHD2000 syringe pump (f_3). The stream from this pump was then mixed with the stream exiting the first reactor and introduced into the second reactor (R_2, t_2). The reaction proceeded at the indicated flow rate for each stream. R_2 was submerged in an oil bath set at the appropriate reaction temperature (T_2). After reaching steady state (2−3 reactor volumes), a sample was collected for 30 min into a beaker containing aqueous NaOAc (2M). In the event that the desired product precipitated from the solution, it was isolated by filtration of the reaction mixture and was washed with water before drying. Otherwise, the reaction mixture was then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were then washed with water (3 × 50 mL) and then brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was then purified by column chromatography *via* the Biotage Isolera 4 (silica-packed 25 g snap column; eluting with the appropriate solvents as indicated below). In some cases, the desired compounds could be isolated without the need for purification by chromatography.

*General Procedure **B** for the Continuous Flow Synthesis of β-Chloroacrylonitriles.* Using the reaction setup as depicted in Scheme 3 and the General procedure **A** for the preparation of the β-chloroiminium salt, an oven-dried screw-top volumetric flask (100 mL), fitted with a Teflon screw-cap, was charged with hydroxylamine hydrochloride (100 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of three times), and DMF was added *via* syringe to make the solution volume 100 mL. The flask was then sonicated to solubilize the reagent, after which the solution was loaded into a plastic syringe and fitted to the system using a fourth Harvard Apparatus PHD2000 syringe pump (f_4) and mixed with the stream exiting the second reactor (R_2, t_2, T_2). The resulting stream was then introduced into a third reactor (653 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.3 mL, R_3, t_3, T_3). The reaction proceeded at the indicated flow rate for each stream. Reactors R_2 and R_3 were submerged in an oil bath set at the appropriate reaction temperature. The products were collected and isolated in the same manner described in General procedure **A**.

*General Procedure **C** for the Continuous Flow Synthesis of Pyrazole Derivatives.* Using the reaction setup as depicted in Scheme 3 and the General procedure **A** for the preparation of the β-chloroiminium salt, an oven-dried screw-top volumetric flask (25 mL), fitted with a Teflon screw-cap, was charged with the acetophenone substrates (6.25−25 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of three times), and DMF was added *via* syringe to make the solution volume 25 mL. This acetophenone solution ([C]) was then loaded into a 30 mL plastic syringe and fitted to a third Harvard Apparatus PHD2000 syringe pump (f_3), and mixed with the stream exiting the first reactor. The resulting stream was then introduced into a second reactor (R_2, t_2, T_2). A second oven-dried screw-top volumetric flask (50 mL), fitted with a Teflon screw-cap, was charged with the arylhydrazine hydrochloride (12.5 mmol) and TFA (15 mmol). A mixture of *Solvent* (THF/water (4:1) or EtOH/water (4:1)) was then added to bring the solution volume to 50 mL. The flask was then sonicated to solubilize the mixture, after which it was loaded into a 50 mL plastic syringe and fitted to the system using a fourth Harvard Apparatus PHD2000 syringe pump (f_4) and mixed with the stream exiting the second reactor. The resulting stream was then introduced into a third reactor (R_3, t_3, T_3). The reaction proceeded at the indicated flow rate for each stream. Reactors were submerged in an oil bath set at the appropriate reaction temperature. The products were collected and isolated in the same manner as that described in General procedure **A**.

Flow Parameters and Analytical Data. *(E/Z)-3-Chloro-3-phenylacrylaldehyde (**4**).* Flow parameters: [C] = 1 M, f_1 = 40 μL/min, f_2 = 50 μL/min, f_3 = 195 μL/min, t_1 = 1.1 min, t_2 = 20 min, T_2 = 80 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = (703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL). The spectral data is in accord with that previously reported.[19]

*(Z)-3-Chloro-3-(3-fluoro-4-methoxyphenyl)acrylaldehyde (**5**).* Flow parameters: [C] = 1 M, f_1 = 40 μL/min, f_2 = 50 μL/min, f_3 = 195 μL/min, t_1 = 1.1 min, t_2 = 20 min, T_2 = 80 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in.), 100 μL, R_2 = (703 cm of PFA capillary tubing (1/16 in. OD ×

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0.04 in.), 5.7 mL). Analysis: mp 94−95 °C; IR (ATR, cm^{-1}): 3045, 1661, 1589, 1510, 1426, 1124, 1017, 800; ^1H NMR (400 MHz, $CDCl_3$) δ 10.15 (d, 1H, J = 6.8 Hz), 7.57−7.44 (m, 2H), 7.00 (t, 1H, J = 8.5 Hz), 6.58 (d, 1H, J = 6.8 Hz), 3.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 152.1 (d, J = 238.6 Hz), 150.8, 150.7 (d, J = 2.6 Hz), 128.1 (d, J = 6.6 Hz), 123.9 (d, J = 3.4 Hz), 123.3, 115.1 (d, J = 20.8 Hz), 113.0 (d, J = 2.2 Hz), 56.4; Anal. Calcd for $C_{10}H_8ClFO_2$: C, 55.96; H, 3.76. Found: C, 55.90; H, 3.78.

(Z)-(4-(1-Chloro-3-oxoprop-1-en-1-yl)phenyl)boronic acid (**6**). Flow parameters: [C] = 1 M, f_1 = 40 μL/min, f_2 = 50 μL/min, f_3 = 97.5 μL/min, t_1 = 1.1 min, t_2 = 30 min, T_2 = 80 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = (703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL). Analysis: mp 190 °C; IR (ATR, cm^{-1}): 3330, 2882, 1648, 1577, 1412, 1341, 1143, 1075, 621; ^1H NMR (400 MHz, d_6-DMSO) δ 10.14 (d, 1H, J = 6.7 Hz), 8.29 (s, 2H), 7.96−7.77 (m, 4H), 7.01 (d, 1H, J = 6.7 Hz); ^{13}C NMR (101 MHz, d_6-DMSO) δ 191.5, 150.8, 135.9, 134.5, 126.1, 124.5; Anal. Calcd for $C_9H_8BClO_3$: C, 51.37; H, 3.83. Found: C, 51.12; H, 3.75.

(E/Z)-3-Chloro-3-(4-chlorophenyl)-2-methylacrylaldehyde (**7**). Flow parameters: [C] = 1 M, f_1 = 20 μL/min, f_2 = 25 μL/min, f_3 = 97.5 μL/min, t_1 = 2.2 min, t_2 = 40 min, T_2 = 80 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = (703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL). Analysis: E/Z: 80/20, IR (ATR, cm^{-1}): 3071, 2895, 1668, 1590, 1487, 1398, 1279, 1093, 835, 682; ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.49−6.93 (m, 5H), 2.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6, 189.6, 152.8, 146.1, 136.8, 136.6, 136.1, 135.8, 134.1, 132.9, 131.3, 129.9, 129.4, 128.8, 14.1, 13.4; Anal. Calcd for $C_{10}H_8Cl_2O$: C, 55.84; H, 3.75. Found: C, 55.82; H, 3.69.

(E/Z)-3-Chloro-2,3-bis(4-methoxyphenyl)acrylaldehyde (**8**). Flow parameters: [C] = 0.5 M, f_1 = 10 μL/min, f_2 = 12.5 μL/min, f_3 = 97.5 μL/min, t_1 = 4.4 min, t_2 = 48 min, T_2 = 80 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = 703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL. Analysis: E/Z: 80/20, IR (ATR, cm^{-1}): 2869, 1678, 1606, 1511, 1245, 1172, 1023, 770; ^1H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.57−7.36 (m, 2H), 7.30−7.15 (m, 3H), 7.07−6.92 (m, 4H), 3.85 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 190.4, 161.8, 160.8, 159.5, 155.0, 139.5, 132.2, 131.9, 131.7, 131.3, 128.1, 126.4, 114.0, 113.9, 113.7, 113.4, 55.6, 55.3, 55.3, 55.2; ; Anal. Calcd for $C_{17}H_{15}ClO_3$: C, 67.44; H, 4.99. Found: C, 67.17; H, 5.15.

(E/Z)-3-Chloro-3-(1H-indol-3-yl)acrylaldehyde (**9**). Flow parameters: [C] = 1 M, f_1 = 80 μL/min, f_2 = 100 μL/min, f_3 = 390 μL/min, t_1 = 2.8 min, t_2 = 10 min, T_2 = 40 °C, R_1 = 61.7 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 500 μL, R_2 = 703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL. Analysis: E/Z: 6/94, IR (ATR, cm^{-1}): 3169, 2988, 1632, 1564, 1426, 1388, 1232, 1133, 1084, 720; ^1H NMR (400 MHz, d_6-DMSO) δ 12.30 (s, 1H), 10.11 (d, 1H, J = 7.0 Hz), 8.24 (d, 1H, J = 3.2 Hz), 7.96−7.82 (m, 1H), 7.54 (dt, 1H, J = 8.2, 0.9 Hz), 7.34−7.13 (m, 2H), 6.73 (d, 1H, J = 7.0 Hz); ^{13}C NMR (101 MHz, d_6-DMSO) δ 190.6, 146.8, 137.8, 132.6, 123.6, 123.2, 122.0, 120.1, 118.7, 113.1, 112.4; Anal. Calcd for $C_{11}H_8ClNO$: C, 64.25; H, 3.92. Found: C, 64.39; H, 3.95.

(Z)-3-Chloro-3-(pyridin-4-yl)acrylaldehyde (**10**). Flow parameters: [C] = 1 M, f_1 = 20 μL/min, f_2 = 25 μL/min, f_3 = 97.5 μL/min, t_1 = 2.2 min, t_2 = 60 min, T_2 = 60 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = 436 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 8.5 mL. Analysis: mp 78−79 °C; IR (ATR, cm^{-1}): 3024, 1671, 1592, 1412, 1216, 1123, 709; ^1H NMR (400 MHz, $CDCl_3$) δ 10.22 (dd, 1H, J = 6.7, 0.5 Hz), 8.73 (ddd, 2H, J = 4.4, 1.7, 0.5 Hz), 7.58 (ddd, 2H, J = 4.4, 1.7, 0.5 Hz), 6.75 (dd, 1H, J = 6.7, 0.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 150.8, 148.9, 142.8, 126.5, 120.6; Anal. Calcd for C_8H_6ClNO: C, 57.33; H, 3.61. Found: C, 56.58; H, 3.79.

(E/Z)-3-Chloro-3-(pyridin-3-yl)acrylaldehyde (**11**). Flow parameters: [C] = 1 M, f_1 = 10 μL/min, f_2 = 12.5 μL/min, f_3 = 48.75 μL/min, t_1 = 4.4 min, t_2 = 80 min, T_2 = 60 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = (703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL. Analysis: mp 45−46 °C; IR (ATR, cm^{-1}): 3014, 2853, 1665, 1603, 1581, 1413, 1236, 1120, 1021, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 10.21 (d, 1H, J = 6.7 Hz), 8.97 (d, 1H, J = 2.4 Hz), 8.71 (dd, 1H, J = 4.8, 1.5 Hz), 8.05 (dt, 1H, J = 8.1, 2.0 Hz), 7.42 (dd, 1H, J = 8.1, 4.8 Hz), 6.70 (d, 1H, J = 6.7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 152.2, 148.9, 147.8, 134.8, 131.8, 125.6, 123.7; Anal. Calcd for C_8H_6ClNO: C, 57.33; H, 3.61. Found: C, 57.07; H, 3.61.

6-Fluoro-4-oxo-4H-chromene-3-carbaldehyde (**12**). Flow parameters: [C] = 0.5 M, f_1 = 40 μL/min, f_2 = 50 μL/min, f_3 = 195 μL/min, t_1 = 1.1 min, t_2 = 20 min, T_2 = 80 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = (703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL. Analysis: mp 151−152 °C; IR (ATR, cm^{-1}): 3069, 1694, 1638, 1564, 1473, 1315, 1133, 720; ^1H NMR (400 MHz, $CDCl_3$) δ 10.36 (d, 1H, J = 0.5 Hz), 8.54 (d, 1H, J = 0.5 Hz), 7.92 (dd, 1H, J = 8.0, 3.1 Hz), 7.57 (ddt, 1H, J = 9.2, 4.2, 0.5 Hz), 7.47 (dddd, 1H, J = 9.2, 7.4, 3.1, 0.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.4, 175.3, 160.8, 160.4 (d, J = 249.8 Hz), 152.5 (d, J = 2.1 Hz), 126.8 (d, J = 7.6 Hz), 123.1 (d, J = 25.4 Hz), 120.9 (d, J = 8.3 Hz), 119.7, 111.4 (d, J = 24.0 Hz); Anal. Calcd for $C_{10}H_5FO_3$: C, 62.51; H, 2.62. Found: C, 62.30; H, 2.44.

7-Chloro-4-oxo-4H-chromene-3-carbaldehyde (**13**). Flow parameters: [C] = 0.5 M, f_1 = 40 μL/min, f_2 = 50 μL/min, f_3 = 195 μL/min, t_1 = 1.1 min, t_2 = 20 min, T_2 = 80 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = (703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL. Analysis: mp >250 °C; IR (ATR, cm^{-1}): 3067, 1707, 1695, 1648, 1606, 1594, 1339, 1166, 889, 764; ^1H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.51 (s, 1H), 8.22 (d, 1H, J = 8.5 Hz), 7.56 (d, 1H, J = 1.9 Hz), 7.46 (dd, 1H, J = 8.5, 1.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.3, 175.3, 160.7, 156.3, 145.9, 141.2, 127.6, 123.9, 120.6, 118.9; Anal. Calcd for $C_{10}H_5ClO_3$: C, 57.58; H, 2.42. Found: C, 57.31; H, 2.30.

(Z)-3-Chloro-3-phenylacrylonitrile (**16**). Flow parameters: [C] = 1 M, f_1 = 40 μL/min, f_2 = 50 μL/min, f_3 = 195 μL/min, f_4 = 390 μL/min, t_1 = 1.1 min, t_2 = 20 min, t_3 = 7.8 min, T_2 = 80 °C, T_3 = 80 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = 703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL, R_3 = 653 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.3 mL. Analysis: mp 34−35 °C; IR (ATR, cm^{-1}): 3060, 2220, 1597, 1575, 1489, 1445, 1229, 676; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.61 (m, 2H), 7.53−7.47 (m, 1H), 7.46−7.39 (m, 2H), 6.02 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 133.8, 131.9, 128.8, 126.7, 115.5, 96.1; Anal. Calcd for C_9H_6ClN: C, 66.07; H, 3.70. Found: C, 65.79; H, 3.94.

*(4-Chloro-2-hydroxyphenyl)(1-(4-chlorophenyl)-1H-pyrazol-4-yl)methanone (**19**).* Flow parameters: [C] = 0.5 M, Solvent = THF/water (4:1), f_1 = 40 μL/min, f_2 = 50 μL/min, f_3 = 195 μL/min, f_4 = 390 μL/min, t_1 = 1.1 min, t_2 = 20 min, t_3 = 7.8 min, T_2 = 80 °C, T_3 = 60 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = 703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL, R_3 = 653 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.3 mL. Analysis: mp 213-214 °C; IR (ATR, cm^{-1}): 3265, 1635, 1595, 1487, 1431, 1261, 850, 770; ^1H NMR (400 MHz, d_6-DMSO) δ 10.77 (s, 1H), 8.77 (s, 1H), 8.07 (d, 1H, *J* = 8.8 Hz), 7.93 (s, 1H), 7.86 (s, 1H), 7.52 (d, 1H, *J* = 8.8 Hz), 7.21 (d, 2H, *J* = 8.5 Hz), 7.05 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (101 MHz, d_6-DMSO) δ 174.3, 155.9, 152.5, 143.9, 138.6, 128.8, 128.2, 127.0, 126.2, 122.2, 122.1, 119.8, 118.6, 113.5; Anal. Calcd for $C_{16}H_{10}Cl_2N_2O_2$: C, 57.68; H, 3.03. Found: C, 57.81; H, 2.95.

*1-(4-Methoxyphenyl)-5-phenyl-1H-pyrazole (**22**).* Flow parameters: [C] = 1 M, Solvent = EtOH/water (4:1), f_1 = 40 μL/min, f_2 = 50 μL/min, f_3 = 195 μL/min, f_4 = 780 μL/min, t_1 = 1.1 min, t_2 = 20 min, t_3 = 5.0 min, T_2 = 80 °C, T_3 = 70 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = 703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL, R_3 = 653 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.3 mL. Analysis: mp 93−94 °C; IR (ATR, cm^{-1}): 1602, 1514, 1254, 1044, 827, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 1H, *J* = 8.8 Hz), 7.70 (d, 2H, *J* = 7.0 Hz), 7.45−7.32 (m, 3H), 7.08−7.00 (m, 3H), 6.89 (dd, 2H, *J* = 9.1, 0.6 Hz), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 137.9, 137.2, 135.7, 132.8, 128.8, 128.5, 126.1, 122.8, 114.9, 114.1, 55.7.

*1-(4-Chlorophenyl)-4,5-bis(4-methoxyphenyl)-1H-pyrazole (**23**).* Flow parameters: [C] = 0.5 M, Solvent = EtOH/water (4:1), f_1 = 10 μL/min, f_2 = 12.5 μL/min, f_3 = 97.5 μL/min, f_4 = 195 μL/min, t_1 = 4.4 min, t_2 = 48 min, t_3 = 17 min, T_2 = 80 °C, T_3 = 80 °C, R_1 = 12.3 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 100 μL, R_2 = 703 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.7 mL, R_3 = 653 cm of PFA capillary tubing (1/16 in. OD × 0.04 in. ID), 5.3 mL, 5 psi back pressure regulator. Analysis: mp 153−154 °C; IR (ATR, cm^{-1}): 2834, 1611, 1493, 1377, 1243, 1030, 951, 798; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.23 (d, 2H, *J* = 8.8 Hz), 7.16 (d, 2H, *J* = 8.8 Hz), 7.11 (d, 2H, *J* = 8.8 Hz), 7.03 (d, 2H, *J* = 8.8 Hz), 6.81 (d, 2H, *J* = 8.8 Hz), 6.78 (d, 2H, *J* = 8.7 Hz), 3.77 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 158.3, 139.9, 138.7, 138.6, 132.7, 131.7, 129.1, 128.9, 126.2, 125.2, 122.2, 122.2, 114.3, 114.0, 55.3; Anal. Calcd for $C_{23}H_{19}ClN_2O_2$: C, 70.68; H, 4.90. Found: C, 70.38; H, 5.01.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental data, analysis and NMR spectra. Descriptions of additional examples. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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