

Continuous-Flow Synthesis of Pyrylium Tetrafluoroborates: Application to Synthesis of Katritzky Salts and Photoinduced Cationic RAFT Polymerization

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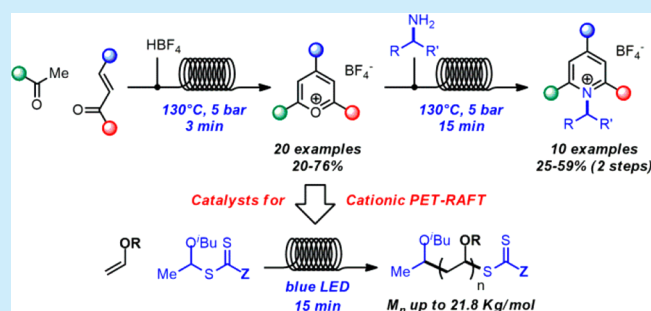
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ABSTRACT: Katritzky salts have emerged as effective alkyl radical sources upon metal- or photocatalysis. These are typically prepared from the corresponding triarylpyrylium ions, in turn an important class of photocatalysts for small molecules synthesis and photopolymerization. Here, a flow method for the rapid synthesis of both pyrylium and Katritzky salts in a telescoped fashion is reported. Moreover, several pyrylium salts were tested in the photoinduced RAFT polymerization of vinyl ethers under flow and batch conditions.

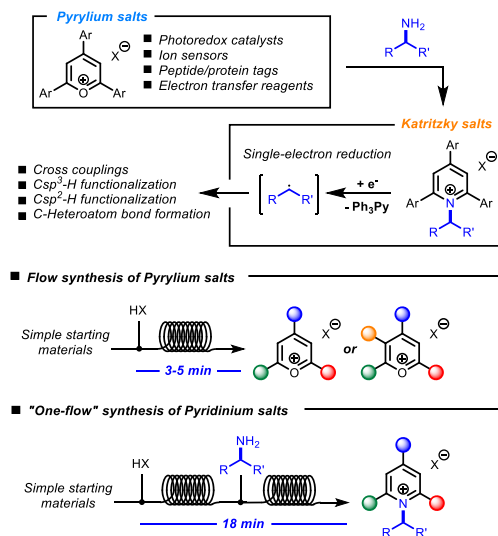


2,4,6-Triarylpyrylium salts have found applications in various fields of chemistry, especially as visible-light photocatalysts for the synthesis of small molecules¹ and photoinduced polymerizations.² In addition to their applications as photocatalysts, pyrylium salts have been used as precursors for a variety of other heterocycles, in particular *N*-alkylpyridinium salts (Katritzky salts), via reaction with primary amines.³ The pyridinium moiety can act in these compounds as a leaving group in nucleophilic substitution reactions⁴ or can lead to fragmentation upon single-electron reduction, generating alkyl radicals. Several methods for the single electron reduction of Katritzky salts have been recently investigated. In particular, activation via metal catalysis,⁵ photoredox catalysis,⁶ and visible light-activated electron donor–acceptor (EDA) interactions⁷ have recently found large interest in the chemistry community.

Based on our interest in flow chemistry and photochemical methodologies,⁸ we developed a flow protocol for the rapid synthesis of pyrylium salts and, in a telescoped fashion, of Katritzky salts, starting from simple starting materials (Scheme 1). As the formation of both pyrylium and Katritzky salts is a thermal reaction, we reasoned that a continuous flow method in superheated conditions would promote much faster reactions than in batch.

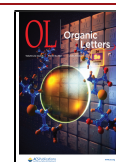
Reversible addition–fragmentation chain transfer (RAFT) polymerization has emerged as a powerful method to generate polymeric materials with controlled properties.⁹ While radical initiation has been traditionally achieved thermally, alternatives have been recently investigated. In particular, the use of photoactivated chain-transfer agents (CTAs) made possible the development of photochemical RAFT methods, which

Scheme 1. Applications of Pyrylium and Katritzky Salts in Chemistry And Outline of This Work



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offer milder conditions and higher degrees of control.^{9b–d} Photocatalytic RAFT polymerizations are often performed in continuous flow conditions, due to the benefits of microflow chemistry in this area.^{8a–c,10}

Pyrylium photocatalysts have been recently used in cationic photoinduced electron/energy transfer RAFT processes (PET-RAFT^{10c,11}) for the polymerization of vinyl ethers,^{2e,f} not always easy to achieve with traditional RAFT.¹² Here, we report investigations on the use of pyrylium salts for the photochemical RAFT polymerization of vinyl ethers in flow and comparison with the corresponding batch process. The use of microflow chemistry allowed for much shorter reaction time, higher molecular weight, and lower polydispersity of the polymeric materials.

Pyrylium salts are typically prepared by reaction of an acetophenone and a chalcone derivative in the presence of an acid. This protocol comprises the use of simple starting materials and allows for the synthesis of both symmetrical and unsymmetrical triarylpyryliums, and was therefore chosen for our investigations in flow. As tetrafluoroborate salts are commonly used for both pyryliums and Katritzky salts applications, we focused on these salts.

We started our investigation by performing the reaction between chalcone (1), acetophenone (2), and HBF₄·Et₂O under flow conditions for the synthesis of 2,4,6-triphenylpyrylium tetrafluoroborate (3) in DCE. The reaction was then optimized with respect to temperature and residence time. Reactions were performed above the boiling point of the solvent (82 °C) using a back-pressure regulator set at 3.4 bar at the end of the reactor coil. Screening of temperature showed 110 °C as the optimal temperature for the reaction, giving up to 74% yield over 5 min residence time (entry 3, Table 1). However, reactions conducted at 130 °C over 3 min residence time gave comparable results (entry 9, Table 1).

The flow protocol was tested for the synthesis of a variety of triarylpyrylium tetrafluoroborates (Scheme 2). Differently

substituted chalcones could be used in the reaction, furnishing halogenated or methoxylated pyryliums 4–8. Different acetophenones, including substituents such as phenyl, methoxy, methylthio, chloro, and bromo, also reacted well, giving products 9–15. Heteroaromatic ketones could also be efficiently employed, and the reaction of chalcones with acetylbenzofuran and acetylbenzothiophene led to pyryliums 16–18. Differently substituted pyryliums, containing alkyl moieties, were then investigated (Scheme 2). Tetrasubstituted and polycyclic pyrylium salts can be prepared by reaction of chalcones with linear or cyclic ketones. For example, indanone, cyclohexa/heptenone, and valerophenone gave pyryliums 19–22 in 68–76% yield.

The yields obtained for the pyrylium salts 3–22 reflect the electronic properties of the reagents, and analogous trends are observed in the literature for batch reactions.¹³ Reactions under batch conditions (same scale, higher concentration, 1 h reaction time) for a few of the salts were performed for the sake of comparison and provided similar yields to the flow protocol, further demonstrating the electronic limitations of the synthesis.

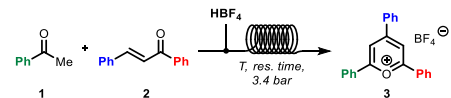
We then set out to investigate the continuous-flow synthesis of *N*-alkyl triphenylpyridinium compounds (Katritzky salts) in a “one-flow” fashion.¹⁴ These compounds are typically prepared in batch by reaction of pyrylium salts with a primary amine in refluxing ethanol for a few hours.^{5a,d,7a} A one-pot process in batch, starting from the synthesis of triphenylpyrylium 3, followed by addition of an amine solution after 1 h of reflux, resulted in the immediate formation of smoke and deposition of amine salts on the walls of flask and condenser and resulted in a complex mixture of salts, making this process cumbersome and unpractical. A telescoped flow synthesis was therefore envisaged, starting with the initial synthesis of pyrylium, followed by immediate reaction with the desired amine.

The use of DCE for both steps resulted in heavy reactor clogging. Ethanol was therefore selected as the solvent of choice for the second step, as it provides a good medium for the synthesis of pyridinium salts, good miscibility with DCE, and a comparable boiling point.¹⁵ The temperature and residence time for the second reactor coil were set respectively at 130 °C and 15 min, making the overall residence time for the two-step process 18 min.

The telescoped protocol was applied to the synthesis of different pyridinium salts (Scheme 3). Pyridinium salts containing linear, primary alkyl chains (23–25) were obtained smoothly in 41–59% yield. Allyl- and benzylamines also reacted with comparable yields (26–28, 44–54%). The reaction with cyclopropylmethyl-, isopropyl-, cyclobutyl-, and cyclohexylamine delivered compounds 29–32, albeit in lower yields (25–37%). As the yield for the triphenylpyrylium precursor 3 (first step) is in average 71%, the second step of the telescoped process results in yields of 58–83% for compounds 23–28. For compounds 29–32, this translates to 35–52% yield. As the reaction of secondary alkyl amines with pyrylium salts (30–32) is known to be much slower than the reaction of primary alkyl amines,¹⁵ we suspect individual optimization might be necessary for these compounds, as well as for 29.

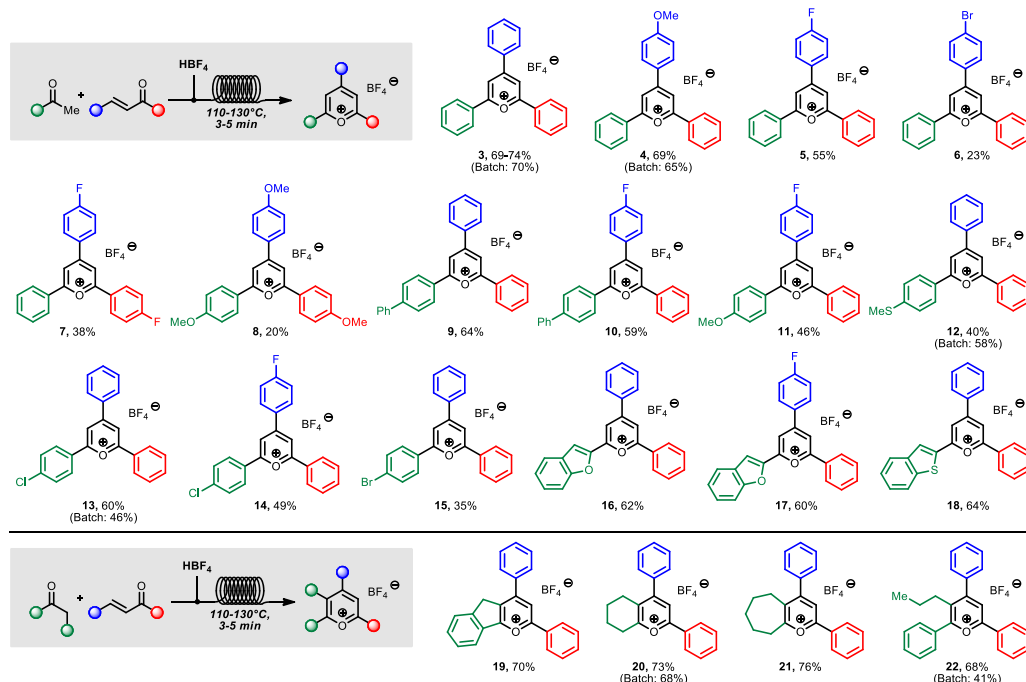
Having established the efficiency of the microflow method for the fast preparation of pyrylium salts, we set out to investigate their use in the photopolymerization of vinyl ethers via cationic RAFT.^{2e,f} We thus selected differently substituted

Table 1. Selected Optimization for the Synthesis of Triphenylpyrylium Tetrafluoroborate in Flow^a

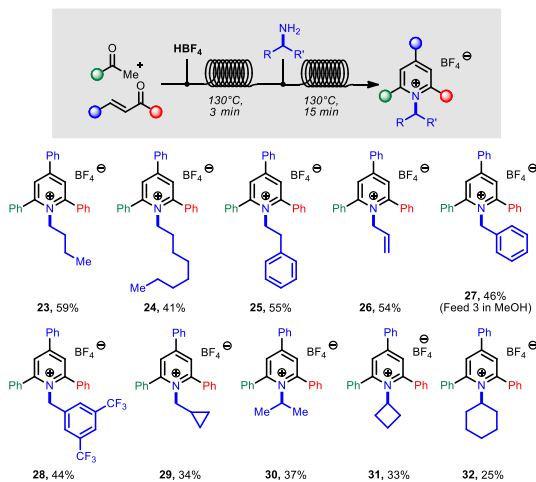


entry	T (°C)	res time (min)	yield (%)
Temperature Screening			
1	90	5	57
2	100	5	65–69 ^b
3	110	5	69–74 ^b
4	120	5	57–67 ^b
5	130	5	63
Residence Time Screening			
6	110	2	57
7	110	3	64
8	110	7	70
9	130	3	69

^aConditions: Feed 1: 2.5–5 mmol of acetophenone, 5–10 mmol of chalcone, diluted with DCE to 2–4 mL. Feed 2: 5–10 mmol HBF₄·Et₂O, diluted with DCE to 2–4 mL. Isolated yields from direct precipitation into Et₂O at the outlet of the reactor. ^bThe reported range represent the variation observed within at least two runs. Conditions in entry 3 were run several times, with results always in the reported range.

Scheme 2. Synthesis of Pyrylium Salts^a

^aConditions: Feed 1: 0.5 g of chalcone (2 equiv), acetophenone (1 equiv), diluted to 2–3 mL with DCE. Feed 2: HBF₄·Et₂O (2 equiv), diluted to 2–3 mL with DCE; T = 110 or 130 °C, P = 3.4–5.2 bar, residence time = 3–5 min. Products were obtained by direct precipitation into Et₂O at the outlet of the reactor, isolated yields after filtration are reported.

Scheme 3. Synthesis of Katritzky Salts^a

^aConditions: Feed 1: 0.5 g of chalcone (2 equiv), acetophenone (1 equiv), diluted to 2–3 mL with DCE. Feed 2: HBF₄·Et₂O (2 equiv), diluted to 2–3 mL with DCE. Feed 3: amine (4 equiv), diluted to 2–3 mL with EtOH; T = 130 °C, P = 3.4–5.2 bar, total residence time = 18 min. Products were obtained by direct precipitation into Et₂O at the outlet of the reactor (isolated yields after filtration and washing), or purified by chromatography.

catalysts 3, 4, 6, 8, and 9 to be tested in the polymerization of benchmark monomers isobutyl vinyl ether (IBVE) and ethyl vinyl ether (EVE) under blue light irradiation. Two different CTAs, based on the xanthate and dithiocarbamate moieties, were also compared. Furthermore, a flow and a batch polymerization protocols were compared to evaluate the benefits of microflow in this process.

As shown in Table 2, the flow process resulted in generally higher molecular weight (M_n , in kg/mol) of the polymers than the batch and a slightly lower polydispersity (D). In addition, while full conversion in flow was obtained after a residence time of 15 min, the batch reaction required several hours of irradiation for completion. While the different catalysts tested generally resulted in similar properties of poly-IBVE and poly-EVE, the effect of the CTA is more remarkable. CTA2 resulted, in general, in higher M_n , albeit with slightly higher D values than CTA1, indicating a somewhat lower level of control on the polymerization. The behavior of catalyst 8 in flow is noteworthy. The combination of catalysts 8 and CTA1 resulted in very poor M_n for both polymers, while, on the contrary, its combination with CTA2 resulted in higher M_n than all the other catalysts. This behavior was observed only under flow conditions. As in flow, the photochemical excitation of the catalyst is much enhanced with respect to batch, we suspect the unusual behaviour of catalyst 8 might be related to a faster activation of CTA2 under these conditions. Catalyst 8 appears to have a very rapid response in the presence of both CTA1 and CTA2.¹⁶ Despite being a less strong oxidant than, for example, catalysts 3,^{2f} the extinction coefficient of 8 at 450 nm is much higher, resulting in a much faster excitation and more frequent electron transfer. This feature would be enhanced under flow conditions, thus explaining our results. We hypothesize that CTA1 can accommodate a faster electron transfer, generating larger amounts of active CTA species, and the formation of more polymeric chains of lower M_n . CTA2, instead, cannot accommodate the electron transfer as efficiently, and a lower amount of radical initiator is generated, giving less, and longer polymer chains. Further investigation will, however, be needed to confirm this hypothesis.

The results obtained (in terms of M_n and D values) for the polymerization of vinyl ethers are in line with previous studies

Table 2. Photoinduced Polymerization of IBVE and EVE under Flow and Batch Conditions^a

entry	cat.	CTA	flow		batch	
			M_n	D	M_n	D
IBVE (R = ^t Bu)						
1	3	1	14.7	1.5	9.9	1.5
2	3	2	19.7	1.8	6.1	2.0
3	4	1	13.4	1.3	10.4	1.3
4	4	2	19.8	1.6	14.1	1.9
5	6	1	15.0	1.3	9.4	1.5
6	6	2	17.6	1.7	11.7	2.3
7	8	1	5.8	1.4	9.2	1.4
8	8	2	21.8	1.6	11.6	2.1
9	9	1	15.8	1.3	2.9	1.4
10	9	2	18.5	1.6	12.9	1.9
EVE (R = Et)						
11	3	1	12.9	1.7	6.8	1.4
12	3	2	11.9	1.7	6.7	2.1
13	4	1	8.7	1.3	5.8	1.6
14	4	2	9.4	1.8	6.9	2.4
15	6	1	8.8	1.8	6.4	1.5
16	6	2	10.8	1.9	9.2	2.2
17	8	1	2.7	1.3	7.3	1.4
18	8	2	15.3	1.7	7.6	2.2
19	9	1	7.9	1.4	3.2	1.3
20	9	2	13.3	1.6	7.5	2.3

^aReactions performed at room temperature in DCM, with 24 W 450 nm LED irradiation. The following molecular equivalents were used: 2000:20:1 (monomer/CTA/catalyst). All experiments were run to full conversion (15 min in flow, 8 h in batch), and the properties were obtained from calibration with polystyrene standards. M_n = kg/mol.

on pyrylium catalysts. Polydispersity values reported in the literature range between 1.08 and 1.98 for IBVE and 1.08 and 1.89 for EVE, indicating comparable control in our experiments, with higher values observed under flow conditions.^{2e,f,17} To our knowledge, no previous photochemical RAFT polymerization of vinyl ethers have been reported under flow conditions. To exclude the possibility of a catalyst-free photoiniferter polymerization, known to occur for example for acrylates and acrylamides,¹⁸ control experiments for the polymerization of both monomers were also performed. Under otherwise identical conditions, the absence of catalysts results in essentially no polymerization, with conversions of 4–10% and M_n values about 50 times lower than with the pyrylium catalysts (see ESI).

In conclusion, we reported here the flow synthesis of a range of pyrylium tetrafluoroborate salts and a two-step flow synthesis of their derivatives *N*-alkylpyridinium salts. The use of flow technology allowed the synthesis of pyrylium salts to be completed in as short as 3 min (1+ hour in batch), while Katritzky salts can be prepared in 18 min (second step alone typically a few hours in batch). Several pyrylium salts were tested in the photochemical RAFT polymerization of vinyl ethers, under batch and flow conditions. The flow protocol resulted in a much shorter reaction time (15 min vs several hours), higher M_n , and lower D of the polymeric materials, compared to the batch procedure. The combination of

photoinduced cationic RAFT polymerization and the use of microflow chemistry is in our opinion a very promising method for the fast, mild synthesis of polymeric materials with controlled properties, and although not fully explored at the moment, we believe its study will attract much interest in the near future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c00178>.

Experimental procedures, further optimization, product characterization, UV–vis data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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