Exploring the Generation and use of Acylketenes with Continuous Flow Processes

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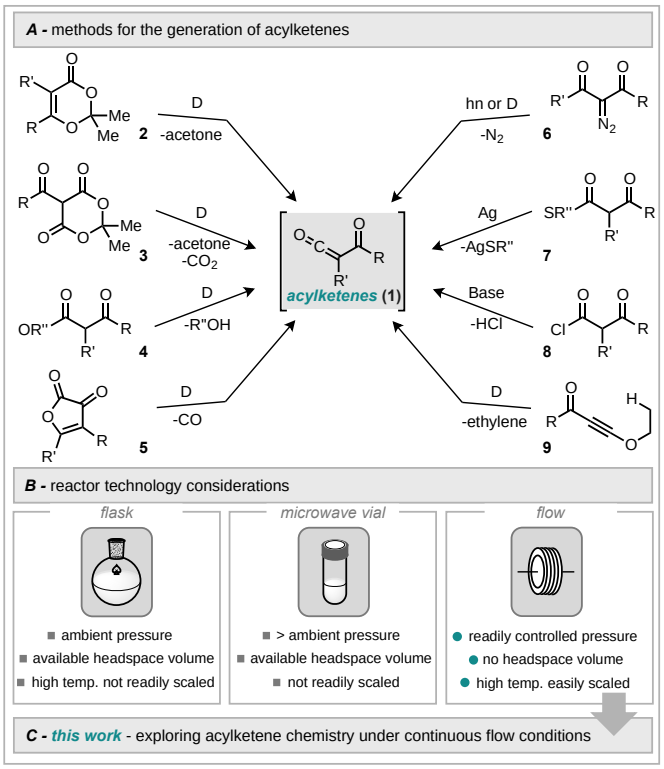
The generation and use of reactive intermediates is well suited to continuous flow processing owing to the ability to scale up reactions, contain hazards and heat solvents past their atmospheric temperature boiling points. Herein we explore the chemistry of acylketenes, generated from commercially available 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (TMD, **10**) under continuous flow conditions. The developed flow chemistry system is capable of permitting a wide range of applications of these acylketene intermediates, including access to equilibrating processes that result in ketone exchange. Some of the dioxinone products resulting from this study are destabilised towards acylketene generation, this is demonstrated through their ability to generate acylketene at lower reaction temperatures.

Introduction.

In 1905, Hermann Staudinger introduced the chemical family of ketenes after treating 2-chorodiphenylacetyl chloride in the presence of zinc.[1] This new class of reactive intermediates were the subject of study for two decades by Staudinger. Ketenes are highly reactive compounds and are normally generated *in situ* and subsequently trapped by other species present in solution. For over a century, researchers have shown impressive creativity in the application of ketene chemistry and several reviews have highlighted the development of their chemistry.[2,3] Ketenes can be functionalised with a plethora of functional groups.[4] Similarly to classical ketenes, acylketenes are highly reactive and widely used in organic synthesis[4] since it was first reported by Wilsmore and Chick in 1908.[5] The half-life of acylketene **1** (R = Me, R' = H) in water is <1 μs and isolable acylketenes, although very uncommon, are only possible for those containing sterically hindered groups, which favour the less reactive *s-trans* conformation.[6,7]

Acylketenes can be generated in a number of ways from a broad range of precursors (A, Scheme 1).[4] For instance, treatment of β-ketoacid chlorides (**8**) under basic conditions; activation of β-ketothioates (**7**) at room temperature with silver; or irradiation of diazo-1,3-dicarbonyls (**6**) with light. However, the most common method to generate acylketenes is *via* thermolysis of 1,3-dioxinones (**2**, **3**), β-ketoesters (**4**), furan 2,3-diones (**5**), or acylated ethoxy alkynes (**9**) (A, Scheme 1). However, all of these methods require high temperatures and generate volatile by-products. Acylketenes participate in a wide range of chemical transformations, examples include [3+2],[8] [2+2][9] and [4+2][10] cycloadditions, nucleophilic addition to generate β-ketoproducts,[11] and Friedel–Crafts acylation reactions.[12] Acylketenes have also been widely used as key intermediates in total syntheses of natural products.[12,13]

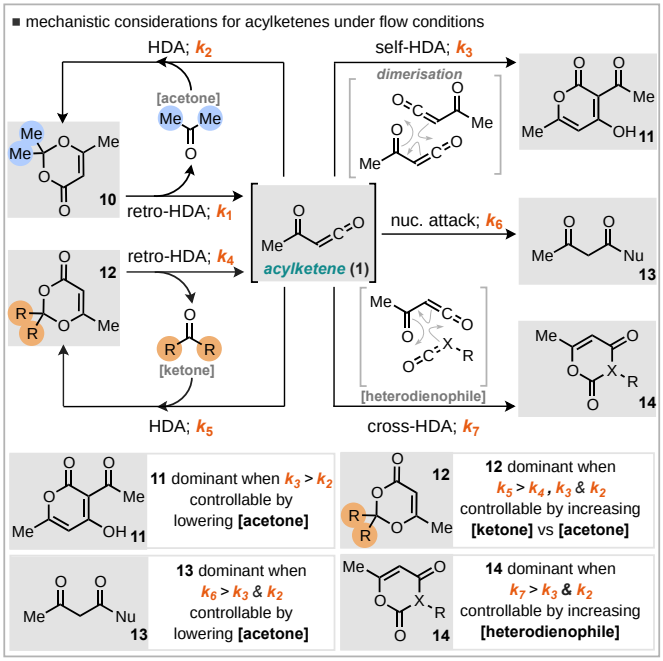


Scheme 1. Common methods for the generation of acylketenes.

Given the requirements for high temperatures and the generation of volatile intermediates, we considered that different reactor technologies could offer alternative and complimentary approaches to studying these interesting reactive intermediates (B, Scheme 1). For instance, traditional flask based processing renders thermolysis reactions for the generation of acylketenes difficult to achieve at scale even in a research laboratory. The pressure and headspace of reactors used for these reactions is also critical to the outcome; the production and removal of volatile by-products is a driving force for equilibrium processes. With this is mind, and our interest in exploring reactive intermediates under continuous flow conditions[15] we envisaged that pressurised flow reactors[Error! Reference source not found.] could offer an opportunity to further

explore the synthetic utility of acylketenes. Indeed, ketenes have been explored under continuous flow conditions previously, with their generation via sigmatropic rearrengment of oxyalkynes, zinc-mediated dehologentation and the use of surrogate keteneiminium salt materials all being reported. [16]

In this study, commercially available 2,2,6-trimethyl-4H-1,3-dioxin-4-one (TMD, **10**) was used as the acylketene precursor. Normally, high boiling point solvents, such as xylene or toluene, are employed in order to generate the acylketene from TMD, which occurs at high temperatures (>150 °C) by a retro-hetero Diels-Alder process.[4]



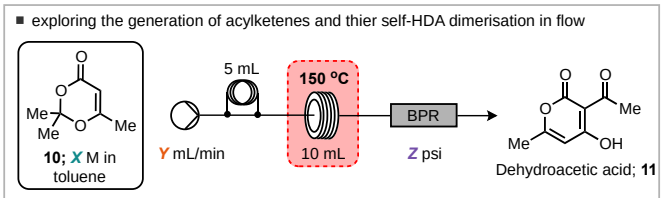
Scheme 2. Equilibrium process between acetone and acylketene.

In this scenario, a pressurised continuous flow setup offers the opportunity of exploring several attributes of acylketene chemistry such as use of lower boiling point solvents such as EtOAc, acetone, Me-THF and a variety of alcoholic solvents which can all be superheated under the processing conditions.[15] It was also envisaged that the ability to run these thermolysis reactions under increased pressure and without headspace would permit the ability to explore equilibria processes and manipulate them through control of reactant concentrations. For example, excision of acetone can generate acylketenes that, in the absence of another reactant, further react through a homo-dimerisation pathway to yield dehydroacetic acid **11** (Scheme 2).[4] However, we considered that in the presence of other volatile ketones (at appropriate concentration), the excision of acetone could be followed by a hetero-Diels-Alder reaction to incorporate the alternative volatile ketone into the dioxinone starting materials (**12**). Moreover, such starting materials may demonstrate different thermal stabilities towards acylketene generation. In the presence of a nucleophile we anticipate the acylketene/TMD equilibrium to be funnelled through to the beta-ketoester product via reaction of the acylketene with a nucleophile, but again this could be dependant on the concentration of acetone. Finally the reactivity of acyl ketenes with heterodienophiles will be explored.

Results and Discussion

1. Control experiments and Dioxinone synthesis

Our study began with the evaluation of dimer formation (**11**) using TMD as starting material and toluene as solvent at 150 °C. A back pressure regulator (BPR) was installed in order to keep the solvent in the liquid phase and the flow system pressurised. The reaction was optimised for concentration, flow rate, and pressure (Table 1). Initially, the flow rate and pressure were kept the same and the concentration varied from 1 to 0.125 M (entries 1-4). 0.5 M was selected as optimal concentration, delivering the dimer in 68% yield (entry 2). Note that, whilst the reaction yield increased by 2% when the concentration was decreased to 0.25 M (entry 3), this was deemed a sub-optimal trade-off of productivity and the increase is within the experimental error. Similarly, doubling the residence time (by halving the flow rate, entries 2 and 5), also resulted in negligible productivity gains. Finally, the pressure of the system was varied. We hypothesised that changing the pressure of the reaction could directly influence the yield of the [4+2] cycloaddition reaction, potentially by possible perturbations on the equilibrium of the retro-HDA and HDA processes.[Error! Reference source not found.] Nevertheless, at the four pressures explored (Table 1, Entries 5-8), 68% yield was observed in all cases and entry 2 was selected as the optimum reaction conditions for further investigation.



Entry	Conc. (*X*)	flow rate (*Y*)	res. time (min)	pressure (*Z*)	Yield of 11 [%][a]
1	1	0.5	20	250	63
2	0.5	0.5	20	250	68 (65)
3	0.25	0.5	20	250	70
4	0.125	0.5	20	250	58
5	0.5	0.25	40	250	70
6	0.5	0.5	20	130	68
7	0.5	0.5	20	40	68
8	0.5	0.5	20	no BPR	68
entries below this line; X = 0.5, Y = 0.5, Z = 250; acetone added to flow input					
Entry	**acetone** (equiv.)		**conversion [%][a]**		**Yield of 11 [%][a]**
9	0		71		68
10	0.125		60		58
11	0.25		49		48
12	0.5		37		34
13	0.75		27		27
14	1		20		20
15	2.5		1		1
16	5		0		0
17	10		0		0

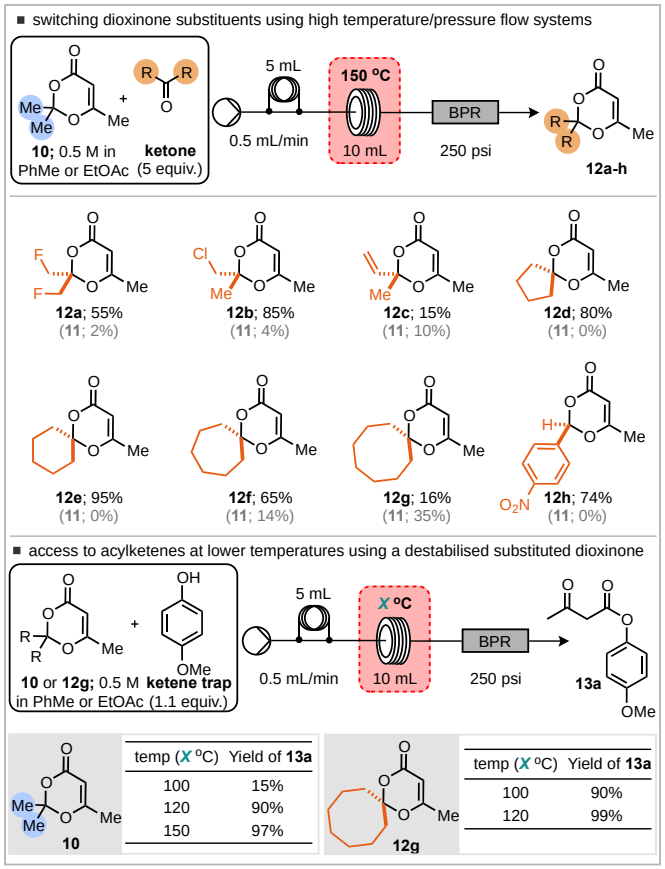
[a] Yield determined by ^{1}H NMR using mesitylene as internal standard, numbers in parentheses represent isolated yields.

Table 1. Optimisation reaction for dehydroacetic acid (**11**) synthesis.

Even in the instance when no back pressure regulator was used, the toluene outgassed and the reaction occurred with an uncharacterised residence time but nonetheless yielded 68% yield of

the dimeric product (Table 1 Entry 8). The higher BPR was selected, for lower boiling point solvents, in preparation for further studies.

The acylketene generating reaction was confirmed to be a reversible process by carefully adding in different quantities of acetone to the starting material input stream (Table 1, entries 9-17). Indeed, the yield of dehydroacetic acid (acetylketene dimer product, **11**) reduced as the number of equivalents of acetone was increased. This observation provided support for an equilibrium process that could be manipulated by controlling the concentration of acetone. Notably, critical to this observation is the use of the pressurised flow system that leaves no headspace for the acetone to escape into the gas phase.

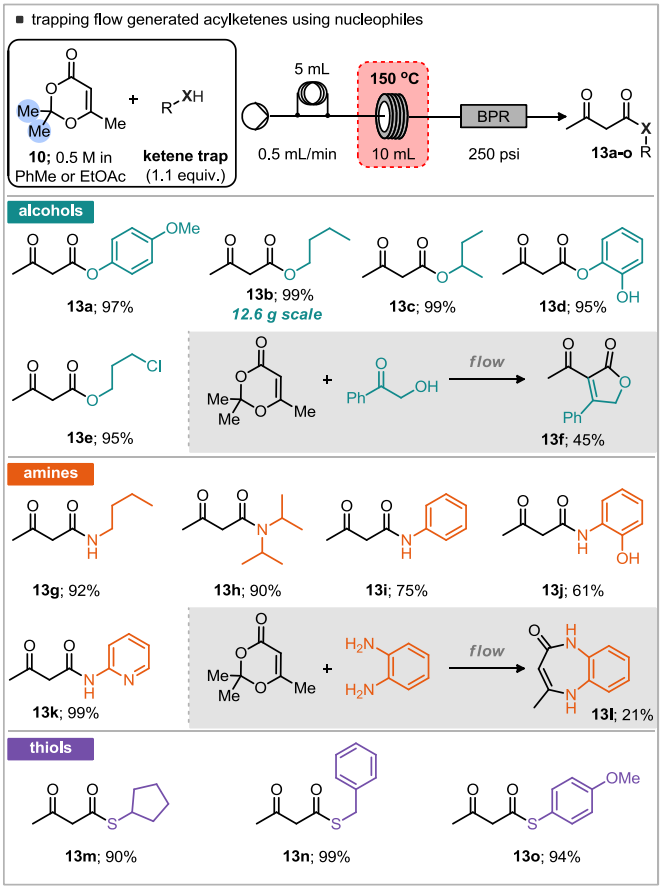


Scheme 3. Dioxinone derivatives synthesis and acylketene formation at lower temperature.

With this observation in mind, the scope of this equilibrating ketone exchange process was explored using a variety of ketone starting materials and applying the conditions described in Table 1, entry 16; with 5 equivalents of added ketone. Several dioxinone derivatives were prepared under the described flow regime (Scheme 3). During these experiments, the presence of dimer **11** was also monitored and significant quantities (≥10%) were observed in the reactions with methylvinyl ketone (MVK), cycloheptanone and cyclooctanone. We hypothesised that the resulting dioxinones, incorporating these ketones may be destabilised towards acylketene generation in comparison to the starting material and therefore result in some dimerization product. This was investigated by preparing and isolating the cyclooctanone derived material (**12g**) and investigating its use for the generation of acylketene at different temperatures (Scheme 3). In the event, a mixture of the dioxinone and 4-methoxyphenol were passed through the pressurised flow coil at a variety of temperatures. Notably at 100 °C, the parent TMD (**10**) afforded 15% of beta-ketoester **13a**, whereas the cyclooctanone derivative **12g** afforded **13a** in 90% isolated yield – demonstrating that indeed it is a destabilised acylketene precursor. We propose that the origin of this destabilisation is due to strain release. The relative order of stability for spiro products was investigated using this crude experimental measure and identified to be **12e** > **12d** > **12f** ≅ **12g** (see Table S1 for further details). Following this investigation, the scope of nucleophiles that could intercept the acylketene was explored under continuous flow conditions.

2. Synthesis of β-ketoesters, β-ketoamides, and β-ketothioates.

β-Dicarbonyls are useful building blocks and are commonly found in the synthesis of natural products and pharmaceutical materials.[18] Several named reactions employ β-dicarbonyl compounds as starting materials, examples include Hantzsch,[19] Biginelli,[20] and Knoevenagel condensation reactions.[21] In view of their significance, several studies have demonstrated synthetic strategies to prepare β-ketoesters,[22] β-ketoamides,[22a,23] and β-ketothioates.[24] In this study, our optimised reaction conditions for the generation of acylketene were applied to the synthesis of β-dicarbonyls using alcohols, amines, and thiols along with TMD (Scheme 4).



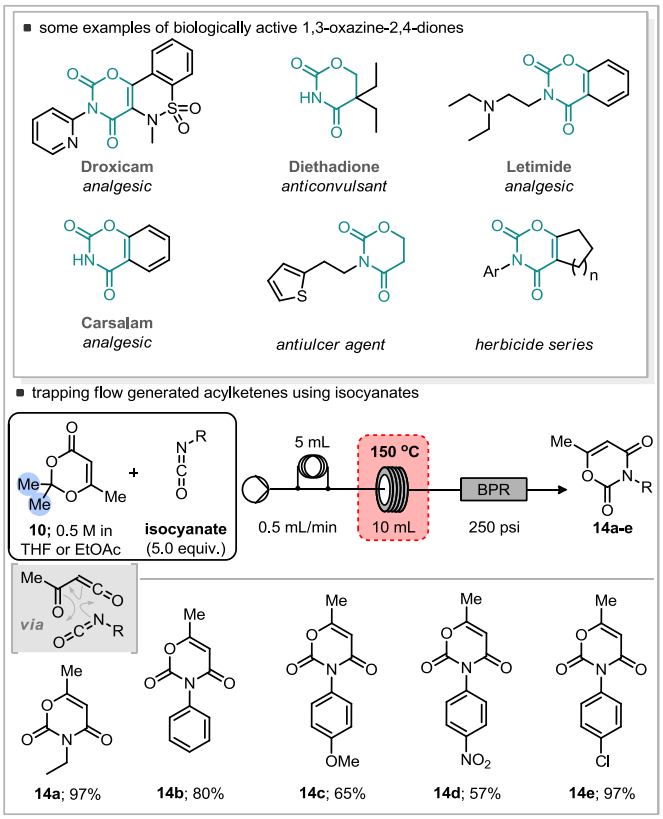
Scheme 4. β-Dicarbonyl compounds synthesis from TMD.

Gratifyingly, the developed flow system is robust and tolerates a range of input substrates without issues of clogging, fouling and

precipitate formation.[15] Excellent yields, ranging from 67% to 99%, were obtained with total conversion of TMD in all cases. For β-ketoamide **13j**, a mixture of ester and amide products were observed, however, the amide was the major product due to the increased nucleophilicity of nitrogen. Use of catechol resulted in β-ketoester **13d** as a single product. However, the use of 1,2 diaminobenzene afforded the bicyclic product **13l**, albeit in 21% yield. Notably, the ambiphilic hydroxy-acetophenone resulted in the formation of bicyclic unsaturated product **13f**, presumably resulting from initial nucleophilic trapping of the acylketene followed by aldol condensation. Trapping with thiols was also readily achieved within the flow reactor. One example in this series, using *n*-butanol as nucleophile, was run as a continuous process (without injection loops) and the resulting product was isolated on a 12.6 gram scale with 98% purity after a simple silica plug purification. This was achieved over 160 minutes and represents a productivity of 30 mmol/hour using a 20 mL coil reactor at 1 mL.min^{-1}.

3. Synthesis of 1,3-oxazine-2,4-diones

1,3-Oxazine-2,4-diones are an important class of molecules which have been studied by several research groups due to their broad spectrum of biological activities. For example, they have analgesic, antiulcer, and antipyretic properties; and have also been used as HIV-1 inhibitors, monoaminoxidase inhibitors, and herbicidal agents (Scheme 5).[25]



Scheme 5. Examples of 1,3-oxazine-2,4-dione active compounds and the respective synthesis of **14a**-**e**.

Asides from the biological activity of these compounds, 1,3-oxazine-2,4-diones find use in organic synthesis as either intermediates or final products.[26] The methods to synthesise the 1,3-oxazine-2,4-dione core include the reaction of a cyclic ketene-*N*,*O*-acetal with chloroformate;[26a] reacting CO_2 with 2,3-allenamides;[26b] β-ketoamides with chloroformate;[26c] using diketene[26d] as well as TMD in the presence of isocyanate in neat conditions or using high boiling point solvents such as xylene or toluene to give moderate yields (21-65%).[26e-g] In our case, the identified flow setup and conditions could be readily applied to the reaction of TMD and isocyanate, however, toluene or xylene were not suitable solvents due to the insolubility of many isocyanates and 1,3-oxazine-2,4-diones. Nevertheless, these solvents could instead be replaced with either ethyl acetate or THF without variation in the reaction yield. Moderate to excellent yields were observed using different isocyanates (Scheme 5).

Conclusions

The use of continuous flow processing was demonstrated for the generation of acylketene species and thier application for the synthesis of dioxinones, β-dicarbonyls, and 1,3-oxazine-2,4-diones. Exploiting the benefits of continuous flow meso-reactors enabled the replacement of high boiling point solvents by greener solvents such as ethyl acetate, without any variation on the reaction yield for all the transformations explored herein. The reported flow conditions are robust and lead to moderate to excellent yields across all of the explored reactions using the same flow rate (0.5 mL.min^{-1}), temperature (150 °C), residence time (20 min), and reaction concentration (0.5 M) for the different studies. In addition, it was demonstrated that the acylketene could be formed at a lower temperature (100 °C) using a TMD derivative (**12g** or **12f**), due to the ring strain caused by the (8,6 or 7,6)-fused ring system. The demonstration of an ability to scale up this chemistry with the same equipment has also been achieved with one substrate being produced on a 12.6 gram scale.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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