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A photochemical flow reactor for large scale syntheses of aglain and rocaglate natural product analogues

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ABSTRACT

Herein, we report the development of continuous flow photoreactors for large scale ESIPT-mediated [3+2]-photocycloaddition of 2-(*p*-methoxyphenyl)-3-hydroxyflavone and cinnamate-derived dipolarophiles. These reactors can be efficiently numbered up to increase throughput two orders of magnitude greater than the corresponding batch reactions.

1. Introduction

Rocaglates are a class of structurally complex secondary metabolites isolated from plants of the *Aglaia* genus.[1–3] Over 100 rocaglates have been isolated or synthesized, all sharing the cyclopenta[*b*]benzofuran core structure (Fig. 1). The naturally occurring family members rocaglamide (**1**), rocaglaol (**2**), silvestrol (**3**), and the synthetic analogue RHT (**4**) possess potent cytotoxicity for a number of cancer cell lines.[4–8] Much of the anticancer activity of these compounds is believed to be derived from translation suppression through inhibition of the RNA helicase eIF4A. However, there have been a number of new and potentially important biological activities reported for the natural products and analogues. Methyl rocaglate (**4**) was found to be a specific inhibitor of TNFα-R or PMA-induced NF-κB activity in T cell lines[4,5,9–13] and rocaglamide was recently reported to inhibit cancer cell migration through Rho GTPase inhibition.[14] In a collaboration with Kramnik and co-workers, we found that the synthetic rocaglate derivatives (**3** and**4**) synergized with low concentrations of IFNγ in primary macrophages to stimulate expression of some IFN-inducible genes, including a key regulatory factor, Irf1, which activates autophagy.[15]

It is clear that the rocaglates have a number of unique biological activities that could lead to novel therapeutics. However, the chemical synthesis of rocaglate natural products and analogues has proven highly challenging.[2,16–18] The common approach leverages an excited-state intramolecular proton transfer (ESIPT)-mediated [3+2]-photocycloaddition to generate aglains (**7**) from 3-hydroxyflavone derivatives (**5**) and dipolarophiles (**6**) which was developed by the Porco laboratory (Scheme 1).[18,19] Subsequent α-ketol rearrangement and hydroxyl-directed reduction affords the rocaglate skeleton (**8**).[20–24]

While this synthetic approach has been widely utilized, there has remained significant challenges related to practicality and scalability of the photochemical cycloaddition. Thus, synthesis of sufficient material to support medicinal chemistry studies of rocaglate analogues *in vitro* and *in vivo* has been a significant hurdle for development of this class of molecule. Herein, we report a numbering up approach for developing a multigram scale continuous flow reactor for ESIPT [3+2]-photocycloaddition.

2. Results and discussion

The ESIPT [3+2]-photocycloaddition of 3-hydroxyflavone (**9**) and methyl *trans*-cinnamate (**10**) to obtain aglain (**11**) is typically carried out in batch, but is difficult to scale due to long irradiation times (typically 12 h), low temperature (0 °C), and high dilution required (30 mM). The typical isolated yield of aglain (**11**) is 40–50% affording on average <150 mg per reaction (Scheme 2a).[20] In 2012, Tremblay and coworkers reported the use of a recirculating flow reactor for synthesis of methyl rocaglate and related

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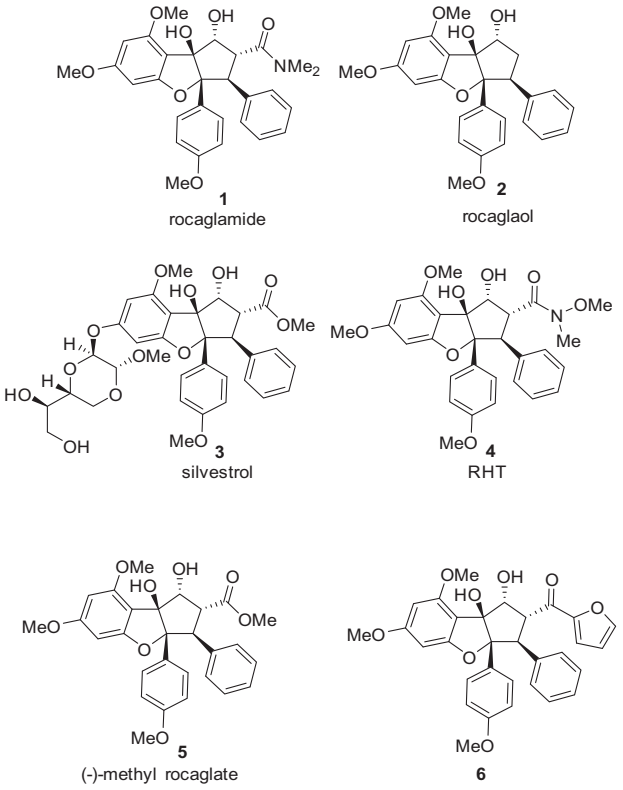


Fig. 1. Biologically active rocaglate natural products and analogues.

derivatives (Scheme 2c). This three-step sequence (photocycloaddition, α-ketol rearrangement, and hydroxyl-directed reduction) was initiated with 3-hydroxyflavone derivative (**11**) and methyl *trans*-cinnamate and gave an overall 20% yield of the methyl rocaglate derivative (**13**) on a 3 g scale.[25] The synthesis of *aza*-rocaglates *via* ESIPT [3+2]-photocycloaddition was also recently reported using a recirculating flow device[26] wherein the *aza*-aglain derivative (**15**) was obtained in 46% over nine hours of irradiation on a 500 mg scale. However, these methods remain limited in terms of scale and throughput.[27] To enable synthesis and medicinal chemistry programs related to the rocaglate scaffolds and to address the challenges of this reaction, we considered a continuous-flow approach which has been demonstrated to be highly beneficial for large scale synthesis of active pharmaceutical ingredients, natural products, and polymers have been reported.[28–31] In particular, photochemical reactions performed in a continuous-flow can be significantly more efficient than the corresponding batch reactions due to better light penetration, resulting in reduced reaction times, cleaner reactions, and greater scalability.[32–38]

2.1. Optimization of ESIPT [3+2]-photocycloaddition in flow

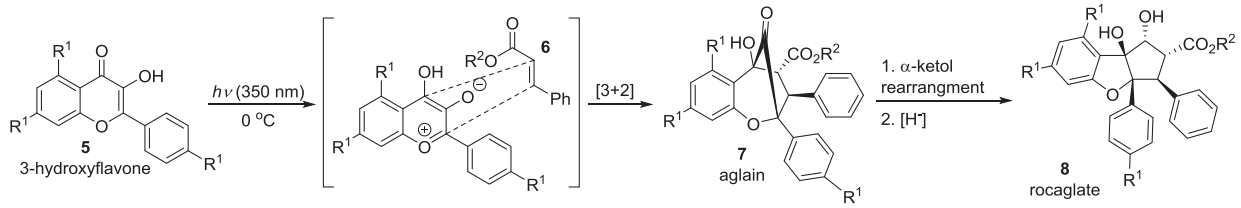
While there have been significant advances in developing flow reactors for large scale photochemical reactions,[39–41] there are still few available options which could be applied to challenging reactions requiring low temperatures and are simple, affordable, and modular. We designed and built a novel flow photoreactor that would enable UV irradiation >300 nm while maintaining a low temperature for the photocycloaddition. The reactor utilizes a 150 W metal-halide lamp (>300 nm) which is placed in the center of a reactor containing wrapped FEP tubing. The inner chamber of the reactor is cooled by recirculation of glycol. We built the first flow reactor (Reactor **A**) using 1/16″ OD FEP tubing resulting in 3.5 mL reactor volume (Fig. 2).

We began optimization of the reaction using 3-hydroxyflavone **9**[25] and methyl cinnamate **10**. Initial reactions revealed that under typical conditions (30 mM) full conversion was observed with only 15-min residence time, compared to 9-h reaction times required for the corresponding batch reaction (Table 1, entries 1 and 2). Increasing the concentration to 60 mM did not affect the reaction and we obtained an increased isolated yield (Table 1, entry 3). In order to maximize the potential throughput and minimize solvent waste, we increased the concentration to 120 mM at which point a longer 30-min residence time was required for full conversion (Table 1, entry 4). Although isolated yields for the flow reactions were slightly lower than the batch reaction these initial efforts resulted in nearly a 20-fold increase in throughput.

Targeting a key intermediate for medicinal chemistry studies, we evaluated the potential for large-scale synthesis of the Weinreb amide-bearing aglain **17** derived from ESIPT [3+2]-photocycloaddition with hydroxamate **16**.[42] Aglain **17** is the precursor to the rocaglate congener RHT, an important tool molecule for studying inhibition of eIF4A, and an intermediate in the synthesis of many analogues including furan **6**. Photoreaction of 3-hydroxyflavone **9** and **16** afforded 47% yield after 9 h irradiation in a batch reactor (Table 1, entry 5) while the flow reaction at 120 mM required 30-min residence time affording a 36% isolated yield (Table 1, entry 6).

To increase the throughput of the reaction, we envisioned a numbering up approach[43] wherein we would daisy-chain reactors rather than splitting the reaction stream into separate reactors.[44] In this way, we would effectively increase the total reactor volume allowing for greater flow rate, and subsequent throughput. We initially combined two reactors (reactor **A**) which effectively doubled the reactor volume to 7 mL (Fig. 3). Reaction of hydroxyflavone **9** and dipolarophile **16** afforded a comparable isolated yield and the reaction throughput was increased from 0.12 g/h to 0.22 g/h. Using this system, we synthesized 890 mg of aglain product **17** in only four hours (Table 2, entry 2). By redesigning the reactor to have a larger surface area, it was possible to increase the volume to 6 mL/reactor (reactor **B**). Using this design, both a single and double reactor afforded similar yield, significantly increasing the throughput to 0.6 g/h (Table 2, entries 3 & 4).

In order to further increase the reactor volume and throughput, we built a new reactor with 1/8″ OD FEP, resulting in a total volume of 12.5 mL for each reactor (reactor **C**). We found that the impact of the longer path length was minimal and we could obtain similar isolated yields with only a slightly longer residence time of 35 min. Numbering up this larger reactor to three (Fig. 3) resulted in a total volume of 37.5 mL, thereby maintaining a 35% yield to



Scheme 1. ESIPT-mediated [3+2] photocycloaddition.