Tetrahedron Letters 59 (2018) 1691–1697

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest paper

Recent advances in the integrated micro-flow synthesis containing photochemical reactions

Yuma Otake [a,b], Hiroyuki Nakamura [a], Shinichiro Fuse [a,*]

[a] Laboratory for Chemistry and Life Science, Institute of Innovative Research, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8503, Japan
[b] School of Life Science and Technology, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8503, Japan

ARTICLE INFO

Article history:
Received 13 November 2017
Revised 6 March 2018
Accepted 7 March 2018
Available online 8 March 2018

Keywords:
Micro-flow
Photochemical reaction
Integrated synthesis

ABSTRACT

Micro-flow photochemical reactions have great advantage over batch photochemical reactions due to its high light-penetration efficiency. Integrated micro-flow reaction enables efficient synthesis of structurally complex compounds from simple starting materials and it can avoid handling of explosive, toxic, unstable, or odorous intermediates. Combination of micro-flow photochemical reactions with integrated micro-flow synthesis enhances their benefits. Here we summarize recently reported integrated multi-step micro-flow synthesis containing various photochemical reactions.

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Introduction

Intensity of light is exponentially attenuated by extending light path length based on Lambert-Beer law. Therefore, the light intensity differs dramatically by distance from the light source in particular using conventional batch reactors. Thus batch photochemical reactions usually require long reaction time and/or high dilution conditions. In addition, in the case of using broadband light source, wavelength also differs by distance from the light source because the longer the wavelength light, the longer it can penetrate into the reaction solution. This sometimes causes undesired photochemical reactions. For these reasons, photochemical

* Corresponding author.
E-mail address: sfuse@res.titech.ac.jp (S. Fuse).

https://doi.org/10.1016/j.tetlet.2018.03.019
0040-4039/

reactions have not been regarded as suitable for large-scale synthesis. In contrast, much attention has been focused on micro-flow photochemical reactions in organic synthesis due to their high light-penetration efficiency.[1] Micro-flow reactors have thin reaction space (≤1 mm) that can suppress the light intensity attenuation, thus, photochemical reactions proceed rapidly and efficiently. Micro-flow photochemical reactions are regarded as promising choices for the large-scale synthesis.

Integration of reactions by combining multiple micro-flow reactors can produce structurally complex compounds from simple starting materials efficiently.[2] Integrated micro-flow synthesis can minimize the number of work-up and isolation steps, thus, generation of wastes can be reduced. In addition, if reaction intermediates are explosive, toxic, unstable, or odorous, reaction integration is valuable because the problematic intermediates can be used to the following reactions without taking them out from the reactors.

Combination of micro-flow photochemical reactions with integrated micro-flow synthesis further enhances their value. Here we summarize recently reported integrated multi-step micro-flow synthesis containing various photochemical reactions.

Two-step micro-flow synthesis containing photochemical reaction

Synthesis of α-trifluoromethyl-substituted carbonyl compounds

Rincón, Kappe and coworkers demonstrated the synthesis of α-trifluoromethyl-substituted carbonyl compound **3** from ketone **1** (Fig. 1).[3] In this synthesis, silyl enol ether **2** was generated from **1** in a micro-flow reactor at first. The generated **2** was mixed with triflyl chloride and injected into a photo reactor which was made with fluorinated ethylene propylene (FEP) tube and a 100 W compact fluorescent lamp (CFL). In this photochemical reaction, Eosin Y was used as an inexpensive photoredox catalyst (0.5 mol%). The desired product **3** was obtained about 20 min.

Eleven α-trifluoromethyl-substituted carbonyl compounds **3a**–**3k** were successfully synthesized from corresponding ketones, as shown in Fig. 2 using the integrated micro-flow reactor.

Chlorination of toluene derivatives and cyclic alkanes

Cantillo, Kappe, and coworkers reported the synthesis of benzyl chlorides **5** via chlorine generation–photochemical chlorination sequence (Fig. 3).[4] In detail, highly toxic and corrosive chlorine gas was prepared and directly used for photochemical reaction safely in a micro-flow reactor. Chlorine gas was generated by mixing 6 M HCl and 1.5 M NaOCl in the first mixer, and dissolved in chloroform in the second mixer. The obtained organic-aqueous biphasic mixture was separated using in line membrane separator. The organic layer was mixed with toluene derivative **4** and introduced into a photo reactor made with FEP tubing (inner diameter: 1.0 mm) and a 75 W medium pressure Hg lamp with a filter (wavelength: >300 nm).

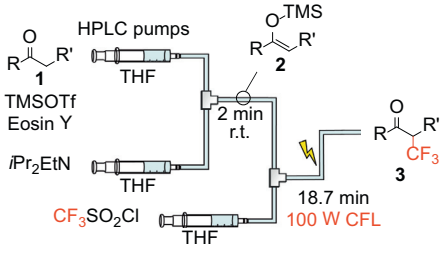

Fig. 1. Integrated micro-flow synthesis of α-trifluoromethyl-substituted carbonyl compounds.

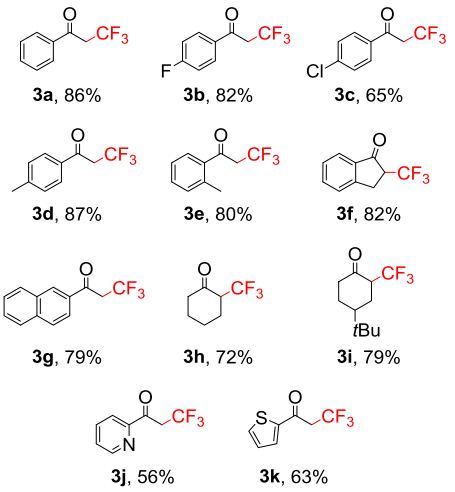

Fig. 2. Synthesized α-trifluoromethyl-substituted carbonyl compounds.

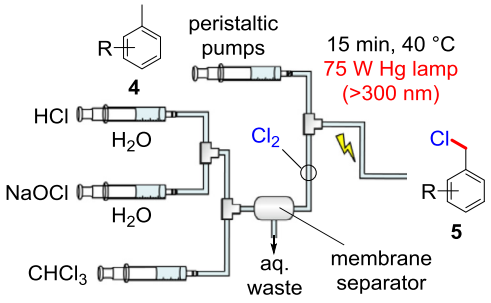

Fig. 3. Integrated micro-flow synthesis of benzyl chloride derivatives.

Four benzyl chlorides **5a–5d** were synthesized by using the integrated micro-flow reactor in excellent yields (Fig. 4). All the reactions were completed in 20 min at moderate temperature. On the other hand, batch reactions typically require several hours of irradiation under reflux condition.

Fukuyama, Ryu and coworkers reported the C–H chlorination of cyclic alkanes **7** (Fig. 5).[5] Chlorine gas was generated from 2 M HCl and 1.9 M NaOCl, and directly mixed with cyclic alkanes **6**. The authors did not use the membrane separator. Photochemical reaction proceeded in a glass-made reactor (depth: 0.50 mm) with a 15 W black light (wavelength: 352 nm) to give desired chlorinated product **7** within 1 min.

Four cyclic alkanes, toluene, ethylbenzene, and cyclohexanone were employed as substrates and afforded the desired chloroalkanes **7a–7g** (Fig. 6).

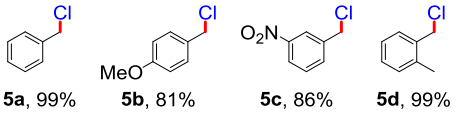

Fig. 4. Synthesized benzyl chloride derivatives.

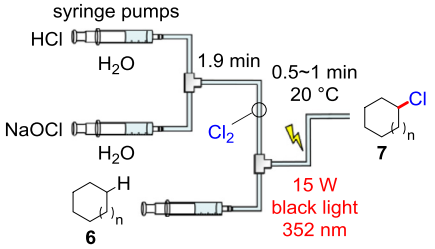

Fig. 5. Integrated micro-flow synthesis of chloro alkanes.