Document type: Article

Accelerated Organic Photoreactions in Flow Microreactors under Gas-Liquid Slug Flow Conditions Using N_2 Gas as an Unreactive Substance

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Received: April 26, 2019; Accepted: June 1, 2019; Web Released: August 24, 2019

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Abstract

In this work, the [2+2] photocycloaddition of carbonyl compounds with olefins, the Paternò-Büchi-type photoreaction, was performed in a flow microreactor under slug flow (two-phase flow) conditions which are constructed by alternatively introducing nitrogen gas as an unreactive substance into the organic reaction phase. The use of N_2 gas-liquid slug flow conditions permitted the organic photoreactions to proceed more efficiently compared to one-phase flow conditions. A detailed investigation of the influence of the flow mode, the viscosity of the solvents, and the segment length (length of each phase) on the efficiency of the photoreaction was conducted. Based on the results, we concluded that these three factors contribute to the improvement in photoreaction efficiency under slug flow conditions using N_2 gas as an unreactive substance. Furthermore, the use of N_2 gas as an unreactive substance was found to be applicable to other Paternò-Büchi-type photoreactions.

Keywords: [2+2] Photocycloaddition | Flow microreactor | Slug flow

1. Introduction

Organic photoreactions that proceed via the excited state permit the production of highly distorted or complex compounds due to the very highly activated excited species.[1] It should be noted in this regard that it is very difficult to produce these types of compounds by conventional thermal reactions because excited species cannot be formed in a thermal reaction process. Thus, the key for organic photoreactions to proceed

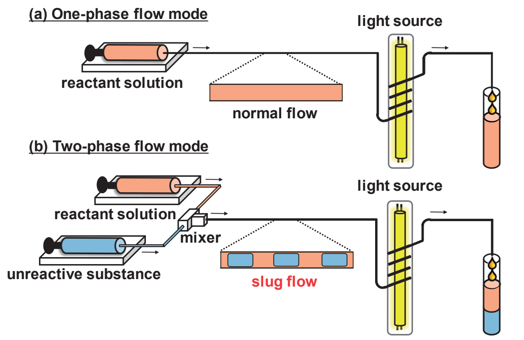


Figure 1. Experimental apparatus for photoreactions using flow tube.

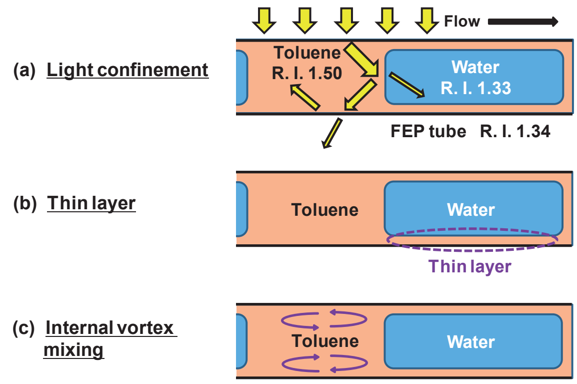


Figure 2. The three factors for highly efficient photoreaction in flow tube. R. I. means the refractive index.

smoothly depends on the efficient generation of such an excited species by light irradiation, in other words, a high level of the absorption of light by substances. The absorption of irradiated light by reactants follows the Beer-Lambert law: $A = \varepsilon \times c \times l$ (where A is the absorbance, ε is the absorption coefficient characteristic of the reactant, c is the molar concentration of the reactant, and l is the length of the optical path). According to this law, reactants near the irradiated surface of a reactor are more easily excited, but, as the reactor becomes larger, it becomes more difficult to irradiate the entire solution. The highly concentrated solutions that are typically used to produce large amounts of products also inhibit the penetration of light. The prolonged irradiation time needed to overcome these problems frequently results in the production of undesired side reactions and over reactions.

A flow microreactor with a narrow flow channel has recently attracted considerable interest in the area of organic photochemistry,[2] because the short path length (l) of such a microreactor allows the reactants to be excited more efficiently. In addition, the flow method can suppress the development of over reaction owing to the long photoirradiation time by discharging the primary products to the outside of the reactor. Therefore, flow reactors are favorable for highly efficient and productive reactions by virtue of the fact that the photoirradiation time can be shortened. Indeed, numerous reports on the use of flow microreactors in organic photoreactions have appeared over the past decade.[3] Our group has also published some reports on the use of flow microreactor techniques in various organic photoreactions.[4] Furthermore, we quite recently developed some highly efficient organic photoreactions under novel slug flow conditions.[5] Slug flow conditions are generally employed in heterogeneous reaction mixtures consisting of a liquid and a liquid or a liquid and a gas phase, both of which are involved in the transformation. On the other hand, the slug flow conditions that we developed consisted of a reactant solution (organic solution) phase and an unreactive substance (a water) phase which does not participate in the photoreaction. Consequently, the slug flow mode using an unreactive substance phase (Figure 1b) resulted in a dramatic increase in both the conversion of a substrate and the chemical yield of a final product, compared to corresponding reactions in a one-phase flow mode (Figure 1a).[5] It was also shown that the slug flow mode resulted in higher productivity.[5b]

In our last report,[5b] we concluded that the improvement in reaction efficiency can be attributed to the following three factors:[6] the light confinement effect[7] in which the light irradiated in the reactor is partially reflected at the interface between the substrate solution segment and the unreactive segment, and between the reactant solution segment and the tube wall because of the difference in their refractive indices (Figure 2a). In this environment, a photon can be confined in a small segment of the organic solution, leading to the very effective excitation of the reactant.

The second factor is the formation of a thin layer of the reactant solution between the water segment and the FEP (fluorinated ethylene-propylene copolymer) tube wall (Figure 2b). Such a thin layer of reactant solution is frequently found in a flow microreactor.[3b,8] For example, Oelgemöller et al. observed a thin layer of a water solution between the air segment and the tube wall, which was made of glass, under slug flow conditions.[9] The formation of a thin layer results in a quite efficient photoirradiation through the extremely short path length.

The third is the effect of internal vortex mixing[10] in a reactant solution segment. The slug flow mode produces an internal fluid vortex, which causes the rapid mixing in each segment (Figure 2c). This internal vortex mixing is a characteristic feature of slug flow conditions and it can accelerate the reaction.

Hitherto, we have concentrated our interest on a slug flow in which water is used as an unreactive substance; however, this slug flow method cannot be applied to reactions of reagents that are soluble in or reactive with water. Herein, we report on the use of N_2 gas as an unreactive substance under slug flow conditions in the [2+2] photocycloaddition of ethyl benzoylformate with 2,3-dimethyl-2-butene, i.e., Paternò-Büchi-type reactions. The use of N_2 gas as an unreactive substance can eliminate the need to separate the unreactive substance from the reaction mixture after the reaction. We also examined the issue of whether the above three factors that improve reaction efficiency are involved in slug flow conditions in which N_2 gas is used in place of water as an unreactive substance. We also performed Paternò-Büchi-type reactions of other substrates under these slug flow conditions.

2. Experimental

2.1 General Considerations. ^{1}H and ^{13}C NMR spectra were recorded using a JEOL JNM-ECP500 spectrometer (500 MHz for ^{1}H NMR, and 126 MHz for ^{13}C NMR). Chemical shifts are reported as δ values in ppm and referenced to the residual solvent peak ($CDCl_3$: δ 7.26 for ^{1}H NMR and δ 77.00 for ^{13}C NMR). The abbreviations used are as follows: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), and m (multiplet). Analytical gas chromatography (GC, Shimadzu GC-2025) was carried out with a ZB-WAX plus column. Helium gas was used as the carrier gas. Melting points were measured using a Yanaco Micro melting point apparatus. Infrared spectra were collected on a JASCO FT-IR-4200 spectrometer. Mass spectra were recorded using a JEOL JMS-700 MStaion [EI-magnetic sector (70 eV), ESI-TOF]. The progress of the reactions was monitored by silica gel thin layer chromatography (TLC) (Merck TLC Silica gel 60 F254). A phosphomolybdic acid ethanol solution was used to detect compounds and a UV lamp was also used to detect compounds. Flash column chromatography was performed using Merck Silica gel 60. If necessary, crude materials were further purified using an LC-908 recycling gel permeation chromatograph equipped with a JAIGEL 2H-40 column (chloroform elution) made by Japan Analytical Industry Co. Spectrograde toluene was purchased from Wako Pure Chemical Industries. Ethyl benzoylformate, 2,3-dimethyl-2-butene, 4,4′-dimethylbenzophenone, 3-methyl-2-buten-1-ol, pentadecane, nonadecane, *m*-xylene, *o*-xylene and 1,2,4-trimethylbenzene were purchased from Tokyo Chemical Industry, Co. Ltd. Triphenylmethane was purchased from Sigma-Aldrich. All of the above reagents were used without further purification. Among them, pentadecane, nonadecane and triphenylmethane were used as an internal standard material for ^{1}H NMR and GC.

2.2 Apparatus for Photoreactions. A 500 W high pressure Hg lamp (USHIO INC.) was utilized as the light source, with a Pyrex immersion well. The reaction setup was placed in a water cooled bath for temperature control (10 °C). For flow conditions, FEP (Nirei Industry Co., Ltd.) tubing (inner diameter (i.d.): 1.0 mm) was employed for irradiation units. FEP tubing was tightly wound around a Pyrex immersion well (Figure 1). The flow rates of both organic solutions containing reactants and N_2 gas were controlled by syringe pumps (YMC Co., Ltd.). A μ-mixer ((MiChS Co., Ltd.) i.d.: 600 μm) was used as a T-shaped connecter.

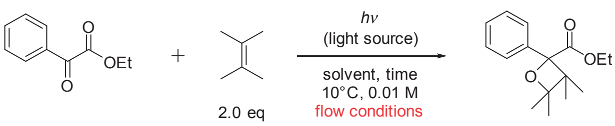
2.3 Photoreactions in a Flow Microreactor. FEP tubing was utilized as an irradiation unit. An appropriate amount of carbonyl compound (0.10 mmol, 0.01 M) and internal standard (0.06 mmol, 0.60 equiv) were placed in a flask, and purged with nitrogen gas for 5 min at room temperature. The solvent (10 mL) in the other flask was also purged with nitrogen gas for 10 min at room temperature, and moved to the first flask via syringe. The olefin (0.20 or 1.0 mmol, 2.0 or 10 equiv) was then added to the solution. This solution was loaded into a gas-tight syringe, and attached to a syringe pump. Nitrogen gas was also loaded into another gas-tight syringe when slug flow conditions were used. T-shaped mixer inlets were connected to both gas-tight syringes, and the outlet was connected to the irradiation unit. The solution and nitrogen gas flow rates and the length of the FEP tube were controlled based on the target irradiation time. After irradiation, conversions and yields were determined by GC or ^{1}H NMR.

2.4 Images of the Flow Conditions. Instant images of the movie of flowing fluid were captured using a Nikon SMZ18 research stereo microscope equipped with a high-speed camera (MEMRECAMfx K5 made by nac Image Technology Inc.). The original movies are included in the supporting information.

3. Results and Discussion

3.1 Examination of Slug Flow Using N_2 Gas. In this work, the Paternò-Büchi type photoreaction of ethyl benzoylformate with 2,3-dimethyl-2-butene was used as a model reaction (Scheme 1).[11] An FEP tube was used as a microcapillary reactor (i.d.: 1 mm) in the experimental apparatus, as shown in Figure 3. A 500 W high pressure mercury lamp (Hg lamp) was employed as a light source. The slug flow was produced through a μ-mixer.

In initial experiments, photoreactions under various flow modes were examined (Table 1). The reaction efficiency was improved when N_2 gas-slug flow conditions were used, similar to water-slug. At the same 10 sec of photoirradiation, when slug flow conditions were used, the conversion was 1.4 times higher



Scheme 1. Paternò-Büchi photoreaction of ethylbenzoylformate with 2,3-dimethyl-2-butene under various conditions.

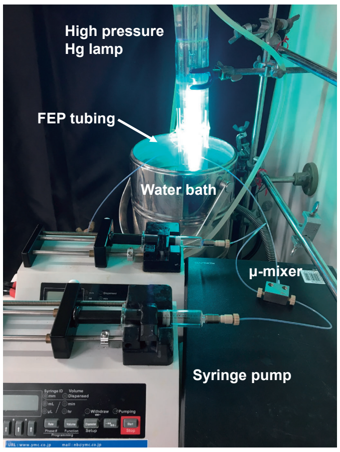


Figure 3. Reaction setup for Paternò-Büchi type photoreactions with the Hg lamp using FEP tube as flow microreactors.

Table 1. Paternò-Büchi photoreactions in toluene using flow microreactors under slug flow conditions with nitrogen gas[a].

Entry	Unreactive Phase	Mode[b]	Conv. (%)[c]	Yield (%)[c]	Improvement Conv.	Improvement Yield
1		One	32	21		
2	Nitrogen	Two	44	30	1.4	1.4
3[d]	Water	Two	55	36	1.7	1.7

a) Photoirradiation time of 10 s, flow rate is the reactant solution:unreactive substance = 1.178 ml/min:1.178 ml/min. b) “One” stands for one-phase flow conditions, “two” stands for slug flow conditions. c) Determined by gas chromatography, average of two runs, internal standard is pentadecane. d) Data from ref 5b.

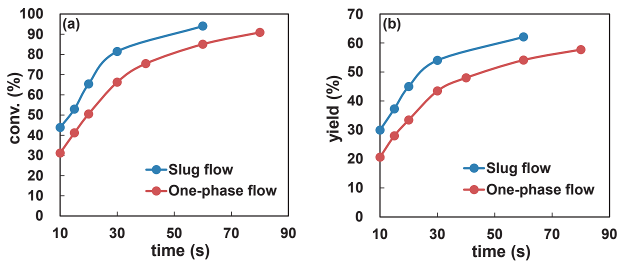


Figure 4. Time course plots of (a) conversion and (b) yield in Paternò-Büchi-type photoreactions under one-phase flow (red line) and slug flow conditions using N_2 gas (blue line).

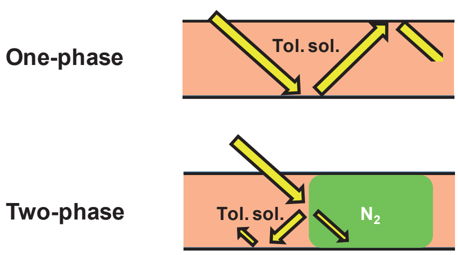


Figure 5. Photoreaction under static conditions (no flow condition). Refractive index of toluene is 1.5, nitrogen gas is 1.0, FEP tube is 1.34.

than when one-phase flow conditions were used (Entries 1 and 2). N_2 gas was found to be applicable as an unreactive substance for the slug flow conditions. In addition, this enhancement was also observed at higher conversions and yields after a more prolonged photoirradiation (Figure 4).

3.2 Examination of Light Confinement Effect. Light confinement through the reflection of the irradiated light should be derived from the difference in the refractive indices between the organic solution segment and the unreactive segment and between an organic solution segment and a flow tube wall (Figure 5). In order to determine whether this phenomenon actually occurred, even when N_2 gas is used as an unreactive substance, we examined the influence of N_2 gas on the efficiency of the slug flow photoreaction under static conditions (no flow mode). Although flow under slug flow conditions generates internal vortex mixing in each segment, this type of mixing can be ruled out when static conditions are used, thus only the light confinement should affect the reaction efficiency.[12] Under two-phase conditions consisting of the reactant solution and nitrogen gas, the solution was photoirradiated without flowing after forming the slug regime. Table 2 includes results of photoreaction of ethyl benzoylformate with 2,3-dimethyl-2-butene under static conditions. Even under static conditions, the two-phase reaction (Table 2, Entry 2) resulted in a higher conversion of the substrate and product yield than the one-phase reaction (Entry 1).

These results show that a part of the irradiated light remains in the organic reaction field through reflected light derived from the difference in refractive indices between the organic solution and N_2 gas (refractive index: toluene 1.49; N_2 1.00; FEP 1.34). In the case of the one-phase mode, the irradiated light partially reflects only at the boundary between the reactant solution and the FEP tube wall, while, in the case of the two-phase mode, it

Table 2. Paternò-Büchi photoreactions in toluene under static conditions with nitrogen gas[a].

Entry	Mode[b]	Conv. (%)[c]	Yield (%)[c]	Improvement	
				Conv.	Yield
1	One	26	17		
2	Two	37	22	1.4	1.3

a) Photoirradiation time of 10 s, length ratio is reactant solution phase:nitrogen gas phase = 1:1. b) "One" stands for one-phase conditions, "two" stands for slug conditions. c) Determined by gas chromatography, average of two runs, internal standard is pentadecane.

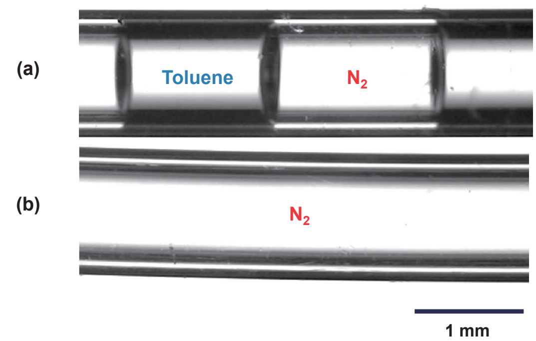


Figure 6. Image taken with a stereomicroscope showing (a) slug flow consisting of a toluene solution and nitrogen gas, length ratio is reactant solution phase:nitrogen gas phase = 1:1. (b) FEP tube with only flowing nitrogen gas.

does so at the boundary between the toluene phase and N_2 gas phase as well as between the toluene phase and the FEP tube wall. As a result, more photons remain in the organic solution segment, even under the two-phase mode using N_2 gas as an unreactive substance. Furthermore, the extent of improvement in the conversion and yield from one-phase flow to two-phase flow under flow conditions were nearly the same, compared to those under static conditions. These results indicate that the light confinement effect affects the reaction efficiency under two-phase flow conditions.

3.3 Examination of the Formation of a Thin Layer. We attempted to directly observe the formation of a thin layer of the organic reaction solution between the N_2 segment and the FEP tube wall, using a stereomicroscope.

Figure 6 shows an image of the direct observation of the slug flow consisting of the reactant solution and N_2 gas. Compared to the state where only N_2 gas flows in the FEP tube (Figure 6b), we were not able to detect clear evidence for the formation of a thin layer of toluene solution (Figure 6a).

On the other hand, we obtained some preliminary results to indicate a thin layer of the reactant solution is actually formed between the N_2 gas segment and the FEP tube. It is well-known that a thin layer of reactant solution is formed between a gas phase and the flow tube wall due to the affinity of reactant solution for the flow tube.[8] Therefore, if a thin layer of a reactant solution were formed, the reaction efficiency would depend on the length of the N_2 gas segment. When the length of the N_2 segment was extended with respect to that of the organic reaction phase at a constant rate, both the conversion of the substrate and the product yield were increased compared to the

Table 3. The Paternò-Büchi photoreactions in toluene using flow microreactors under slug flow conditions with various nitrogen gas segment length[a].

Entry	Mode[b]	Segment Length (mm)[c]	Conv. (%)[d]	Yield (%)[d]	Improvement	
					Conv.	Yield
1	One		32	21		
2	Two	1:1	44	30	1.4	1.4
3		1:3–4	54	38	1.7	1.8
4		1:5–6	50	35	1.6	1.7
5		1:12–15	49	35	1.5	1.7

a) Photoirradiation time is 10 s. b) "One" stands for one-phase flow conditions, "two" stands for slug flow conditions. c) Length ratio is reactant solution:nitrogen gas. d) Determined by gas chromatography, average of two runs, internal standard is pentadecane.

result of the one-phase flow reaction (Table 3). However, this improvement in conversion and yield did not increase when the N_2 gas segment length exceeded 3–4 mm. Detailed studies concerning this observation are currently underway. These results suggest that a thin layer of reactant solution may be formed between the nitrogen gas phase and the FEP tube wall.

3.4 Examination of an Internal Vortex Mixing Effect. It is well-known that high speed mixing can occur in flow microreactors due to the presence of narrow channels.[10] Under slug flow conditions, there is difference in flow velocity between the center of the stream and the vicinity of the tube wall, resulting in highly efficient stirring accompanied by an internal fluid vortex in each segment.[10c] Such an environment would be predicted to increase the frequency of collisions of all reactants and, as a result, would accelerate the intermolecular reaction. Stirring efficiency is dependent on the viscosity of the solvent:[13] The lower the viscosity of the solvent, the higher will be the mixing rate inside the reaction field. We investigated the influence of solvent viscosity on the efficiency of the photoreaction under the conditions of Entry 3 in Table 3. Four kinds of solvents with similar refractive indices but different viscosities were examined to make the influence of light confinement almost identical in all the solvent.

As shown in Figure 7, improvement value of product yield decreased with increasing solvent viscosity. Thus, from these results, the effect of internal vortex mixing in the reaction field is clearly related to the reaction efficiency.

3.5 Applications to Other Paternò-Büchi Type Organic Photoreactions. We next examined the present slug flow method using N_2 gas to other Paternò-Büchi-type reactions.

Results for the reactions of 4,4′-dimethylbenzophenone,[14] instead of ethyl benzoylformate, as a substrate in a [2+2] photocycloaddition reaction are shown in Table 4. The reaction under slug flow conditions (Entry 2) proceeded more efficiently to give the corresponding oxetane derivative than one-phase flow conditions (Entry 1). Furthermore, when the reaction time (irradiation time) was extended to 180 seconds, this photoreaction produced a product yield of 54% (Entry 3).

When ethyl benzoylformate was reacted with 3-methyl-2-buten-1-ol[15] under a similar slug mode, the reaction proceeded more efficiently to give a higher yield of the cycloaddition product than was obtained when the one-phase flow mode was

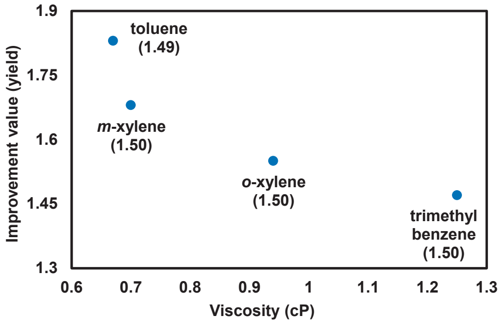
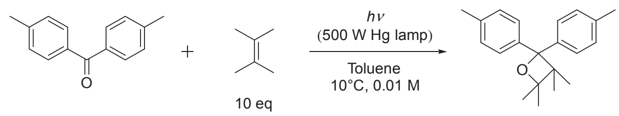


Figure 7. Yield improvement versus solvent viscosity. The numbers in parentheses show the refractive index of solvents. Length ratio is reactant solution phase:nitrogen gas phase = 1:3–4. Photoirradiation time is 10 s.

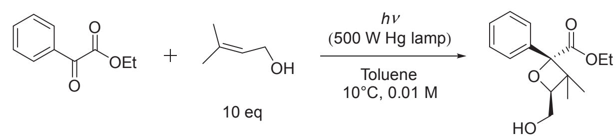
Table 4. Paternò-Büchi photoreactions using 4,4′-dimethylbenzophenone and 2,3-dimethyl-2-butene in flow microreactors under slug flow conditions with nitrogen gas[a].



Entry	Mode[b]	Irr. Time (sec)	Conv. (%)[c]	Yield (%)[d]	Improvement	
					Conv.	Yield
1	One	30	32	16		
2	Two	30	49	26	1.5	1.6
3		180	96	54		

a) Flow rate is the reactant solution:nitrogen gas = 1.178 ml/min:1.178 ml/min. b) "One" stands for one-phase flow conditions, "two" stands for slug flow conditions. c) Determined by ^{1}H NMR, average of two runs, internal standard is nonadecane. d) Determined by gas chromatography, average of two times, internal standard is nonadecane.

Table 5. Paternò-Büchi photoreactions using ethyl benzoylformate and 3-methyl-2-buten-1-ol in flow microreactors under slug flow conditions with nitrogen gas[a].

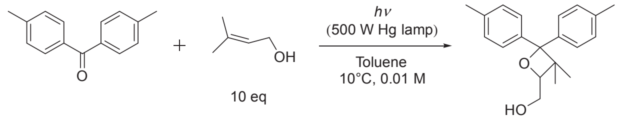


Entry	Mode[b]	Irr. Time (sec)	Conv. (%)[c]	Yield (%)[c]	Improvement	
					Conv.	Yield
1	One	10	54	19		
2	Two	10	76	31	1.4	1.6
3		100	100	40		

a) Flow rate is the reactant solution:nitrogen gas = 1.178 ml/min:1.178 ml/min, steric configuration of product is determined from NOESY analysis. b) "One" stands for one-phase flow conditions, "two" stands for slug flow conditions. c) Determined by ^{1}H NMR, average of two runs, internal standard is triphenylmethane, this internal standard added after photoreaction.

used (Table 5). The reaction of 3-methyl-2-buten-1-ol is characteristic of the present flow mode, because 3-methyl-2-buten-1-ol is water-soluble and therefore not applicable to slug

Table 6. Paternò-Büchi photoreactions using 4,4′-dimethylbenzophenone and 3-methyl-2-buten-1-ol in flow microreactors under slug flow conditions with nitrogen gas[a].



Entry	Mode[b]	Irr. Time (sec)	Conv. (%)[c]	Yield (%)[c]	Improvement	
					Conv.	Yield
1	One	10	32	16		
2	Two	10	43	25	1.3	1.6
3		100	98	54		

a) Flow rate is the reactant solution:nitrogen gas = 1.178 ml/min:1.178 ml/min. b) "One" stands for one-phase flow conditions, "two" stands for slug flow conditions. c) Determined by ^{1}H NMR, average of two runs, internal standard is nonadecane.

mode reactions where water is used as an unreactive substance. The product was obtained as a single diastereomer possessing a ($2R^*$,$4R^*$) configuration. The substrate was consumed within one hundred seconds of photoirradiation to give the product in 40% yield.

The [2+2] photocycloaddition of 4,4′-dimethylbenzophenone with 3-methyl-2-buten-1-ol was also examined (Table 6). In this case, the slug flow mode (Entry 2) was superior to the one-phase flow mode (Entry1) in terms of substrate conversion and product yield. Increasing the photoirradiation time to 100 seconds improved the yield to 54% with the substrate being nearly converted. All of the above results indicate that the slug flow method using N_2 gas can be applied to various organic photoreactions and result in an increased efficiency.

4. Conclusion

In conclusion, the Paternò-Büchi-type photoreaction of ethyl benzoylformate with 2,3-dimethyl-2-butene was performed in a flow microreactor using N_2 gas as an unreactive substance. N_2 gas can be used as an unreactive substance as well as the water-containing flow mode reported previously. As evidenced by using no flow conditions, we conclude that the light confinement effect is an effective factor for improving reaction efficiency under the present slug flow mode. In addition, although a thin layer of the toluene phase was not directly observed by stereomicroscopy, experiments in which the segment lengths were changed are consistent with a thin layer of toluene solution being formed in the reaction. Based on results of reactions in solvents with various viscosities, we conclude that internal vortex mixing is also an additional factor for improving reaction efficiency. From the above results, we conclude that the three effects function synergistically to improve the photoreaction efficiency under slug flow conditions using the N_2 gas as an unreactive substance. It was also demonstrated that the present flow mode is effective for a variety of Paternò-Büchi-type reactions and results in improved reaction efficiency.

This work was supported, in part, by a Grant-in-Aid for Young Scientists (B) (No. 25870437, JP16H04333), a Grant-in-Aid for Scientific Research (B) (No. 24310101, JP15H03544) from the Japan Society for the Promotion of Science (JSPS), and a Grant-in-Aid for Scientific Research on Innovative Areas in Middle Molecular strategy (JP18H04414) from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT). M. N. is grateful to the NAIST Presidential Special Fund for supporting this research. In addition, this work was supported by JKA and its promotion funds from KEIRIN RACE. We would like to thank Industrial Technology Center of Wakayama Prefecture (WINTEC) for the stereomicroscopes measurement.

Supporting Information

The supporting information contains experimental details including NMR analyses and characterization of compounds. This material is available on https://doi.org/10.1246/bcsj.20190117.

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