

Pulsed light induced trifluoromethylation of 1,3-dimethoxybenzene: A frequency controls chemoselectivity and chemical yield

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Abstract

We developed a new methodology for photo-induced trifluoromethylation reaction of 1,3-dimethoxybenzene by using pulsed light irradiation. We also found that the frequency of pulsed light affected the regioselectivities and chemical yields of this reaction. The optical parameters of pulsed light expected to be important topics for optimizing and controlling reactions.

Introduction

Introduction of fluorine atom into the chemical compound can significantly change its properties, such as increasing its metabolic stability and enhancing its biological activity, which is often seen in pharmaceuticals and agrochemicals.¹ Particularly, the trifluoromethyl (CF₃) group has attracted much attention because of its strong electron-withdrawing nature and increasing lipophilicity, which greatly affects the pharmacological activity of chemical compounds, in addition, it is an alternative substituent of comparable size that does not significantly change the binding affinity.² Methods of introducing the CF₃ group have been developed rapidly over the past 20 years and many photo-induced trifluoromethylation reactions have been reported recently,³ starting with the visible light-induced trifluoromethylation reaction of arenes and heteroarenes using a photoredox catalyst reported by Macmillan et al. in 2011.⁴ For the synthesis of such CF₃-containing compounds, in addition to the development of catalysts and the establishment of methodologies, it is important to develop suitable light sources and reaction apparatuses.⁵ Continuous light was generally used for most of photochemical reactions, however, as one method for optimizing the light source, pulsed light that can control the photon concentration per unit time by intermittent light irradiation is conceivable. Pulsed light has been applied in various fields by varying the frequency and duty ratio which can control the ON/OFF time ratio, for example, to improve the efficiency of photosynthesis,⁶ skin rejuvenation,⁷ and decontamination (Fig.1).¹⁸

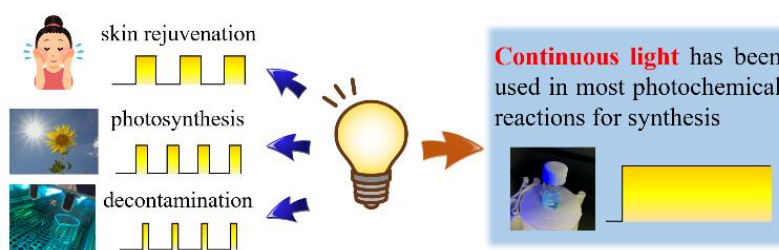
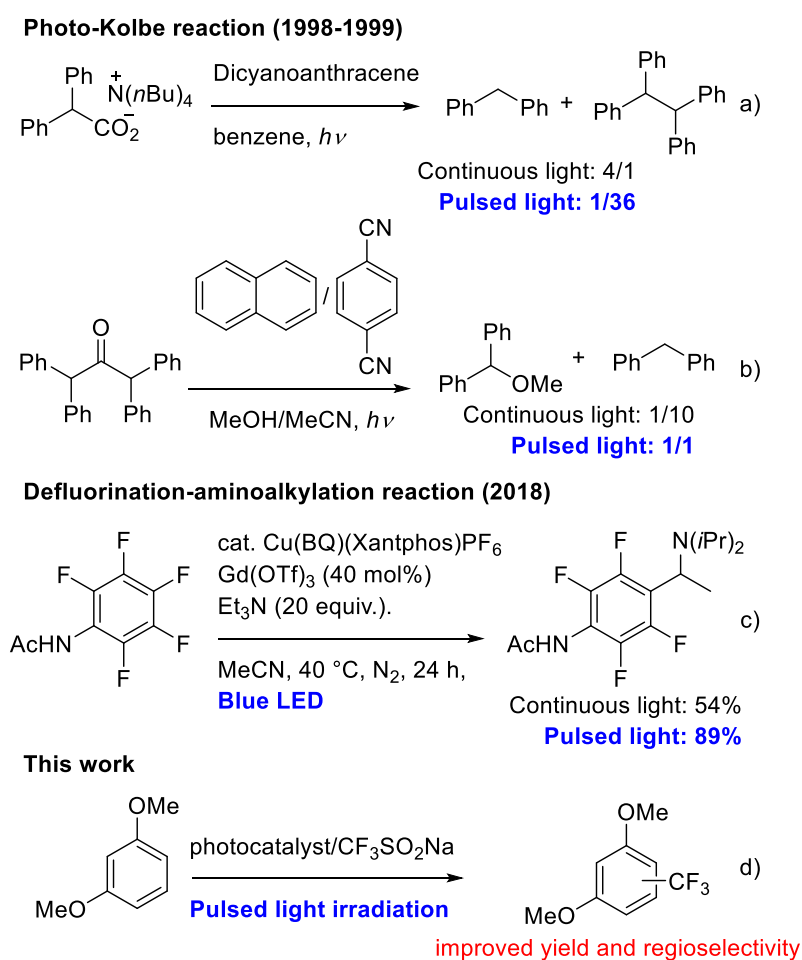


Fig. 1 The utilities of pulsed light irradiation in various field.

On the other hand, although pulsed light is used as a means of analysis in the field of chemistry, there are only a few cases in which pulsed light is used as a light source for synthetic reactions. In 1999, Sawaki *et al.* found that the main product was changed when continuous and pulsed light were used in the Kolbe reaction (Scheme 1a and 1b).^{11,12} They mentioned that a possibility of controlling the chemoselectivity of the reaction

by the method of light irradiation in their report. In 2018, the use of pulsed light for the aminoalkylation reaction of fluoroarenes was also reported by A. C. Bissember et al.. The pulsed light irradiation improved the yield of the reaction with higher frequency (Scheme 1c).¹³ They surmised that an excited state lifetime of copper catalyst and frequency of pulsed light approximately matched, resulting in increased yields. Encouraged by these findings, we considered that the use of pulsed light would improve the selectivity of reactions, and if the parameters of light source could be treated as an item to be evaluated as well as reaction conditions such as catalysts, reagents and temperature, it might lead to simplification of the reaction, eliminating the need to investigate complicated reaction conditions. Hence, we initiated this study to enhance the utilization of pulsed light for photo-induced chemical reactions and to make it a new methodology that could be applied to trifluoromethylation reactions. (Scheme 1d).



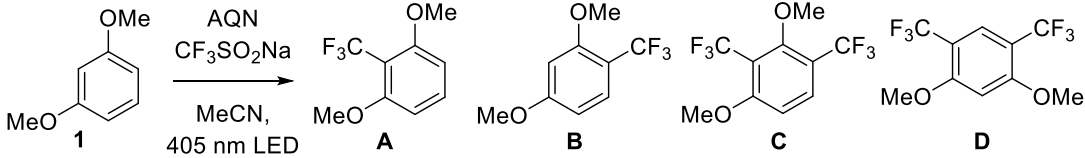
Scheme 1. The potential for using pulsed lights in photo-induced chemical reactions.

Results and Discussion

We first performed a slightly modified photo-induced trifluoromethylation reaction of aromatic rings which is useful and has simple reaction condition, reported by Ito et al. in 2014,¹⁴ using 1,3-dimethoxybenzene (**1**) as substrate, $\text{CF}_3\text{SO}_2\text{Na}$ (2.2 equiv.) as trifluoromethylating agent, anthraquinone (AQN, 5 mol%) as photocatalyst in acetonitrile to ensure quantification of the light irradiation was employed by same 405 nm LED with intensity of 235 mW/m^2 for 20 h at room temperature. To further improve reproducibility of the reaction, the light source was positioned 20 mm from the surface of the reaction solution so that the reaction mixture was uniformly irradiated with light, and the reaction temperature was maintained using a water bath, finally (for details, see: Fig. S1 and S2).

The reaction proceeded and gave a mixture of 1,3-Dimethoxy-2-(trifluoromethyl)benzene (**A**) and 2,4-Dimethoxy-1-(trifluoromethyl)benzene (**B**), 1,3-Dimethoxy-2,4-bis(trifluoromethyl)benzene (**C**), and 1,5-Dimethoxy-2,4-bis(trifluoromethyl)benzene (**D**) in 84% yield and the product ratio in 16/52/5.0/11 (Table 1, entry 1). On the other hand, irradiation with pulsed light at a frequency of 100 kHz and duty ratio 0.1 that means a period of 1 μ s on time and 9 μ s off time for 20 h yielded 86% and products **A**, **B**, **C**, and **D** were obtained at a ratio of 18/59/1.8/6.7, respectively (Table 1, entry 2). We considered the thermal effect on the reaction and set the reaction temperature 15 $^{\circ}$ C to minimize and uniform that influence. The results of the reaction using continuous light and pulsed light, respectively, showed that continuous light improved the yield up to 90% and the product ratio of 18/57/4.4/11, while pulsed light also improved the yield and the target compounds were obtained with 94% yield at a product ratio of 19/66/2.1/6.6 (Table 1, entries 3 and 4). Next, when the total irradiation time were adjusted to match those of the pulsed light by setting the continuous light irradiation time to 2 h, we found that the selectivity of the products was increased although the reaction yield was significantly decreased (Table 1, entry 5, 31% yield and selectivity with 5.0/25/0/0.6). When the intensity of continuous light was reduced to 10% with the reaction time of 20 h for arranging only the total light intensity, the result was comparable to those obtained with pulsed light irradiation (Table 1, entry 4 vs. 6). We also observed that the reaction did not proceed in the absence of light irradiation (Table 1, entry 7).

Table 1. Optimization of the reaction conditions.^a



entry	light condition	temp. ($^{\circ}$ C)	time (h)	yield (%) ^b	A/B/C/D ^b
1	Continuous light	r.t. ^c	20	84	16/52/5.0/11
2	Pulsed light (100k Hz, duty ratio = 0.1)	r.t. ^c	20	86	18/59/1.8/6.7
3 ^d	Continuous light	15	20	90	18/57/4.4/11
4	Pulsed light (100k Hz, duty ratio = 0.1)	15	20	94	19/66/2.1/6.6
5	Continuous light	15	2	31	5.0/25/0/0.6
6	Continuous light, intensity = 10% ^e	15	20	92	20/64/1.8/5.8
7	No light	15	20	N.R.	-

^a Reaction condition: **1** (0.25 mmol), CF₃SO₂Na (0.55 mmol) and AQN (0.0125 mmol) in acetonitrile (2.5 mL) at corresponding temperature and irradiation time. ^b determined by ¹⁹F NMR. ^c 21 to 25 $^{\circ}$ C. ^d Average of three reactions. ^e 23.5 mW/m².

It is noteworthy that the reaction conditions using pulsed light, continuous light for 2 h, and continuous light with 10% intensity all have the same total light intensity (Table 1, entries 4, 5, and 6). From a frequency point of view, the reaction condition that 2 h of continuous light irradiation can be regarded as one cycle of pulses with an ON time of 2 h and an OFF time of 18 h, and the frequency can be represented as 1.4×10^{-5} Hz (Table 1, entry 5). Compared to the reaction condition at 10^5 Hz (a period of 1 μ s on time and 9 μ s off time, Table 1, entry 4), the improvement of selectivity was observed albeit the lower yield (Table 1, entry 4 vs 5), namely, it can be seen that the yields and product ratios vary depending on the length of ON time and OFF time in spite of the same total irradiation time. These results imply that frequency, a parameter that determines the irradiation time, is an important factor affecting this reaction. On the other hand, 1/10 light intensity (23.5 mW/m²) gave similar results to pulsed light at 10^5 Hz (Table 1, entry 6 vs 4). This indicates that it is difficult to achieve both high yield and high selectivity by simply reducing the photon concentration uniformly. Based on the above, we considered that there was a possibility of finding a region where selectivity

of the reaction can be controlled with maintaining the yield by controlling the frequency. For the purpose of clarifying the effect of frequency in this reaction, we decided to carefully evaluate the correlation of reaction yield and product selectivity with frequency shifted by one order of magnitude at a time between reaction conditions of 1.4×10^{-5} Hz and 10^5 Hz. All reactions at the frequencies from 10^{-4} to 10^4 Hz were performed with the same parameters (duty ratio, total reaction time, and total irradiation time, were fixed at 0.1, 20 h, and 7200 sec, respectively.) (Fig. 2). The product ratio of mono-trifluoromethylated compound **A** increased up to 10^{-3} Hz (a period of 100 sec on time and 900 sec off time), after which the yield reached a peak and there was almost no effect on the yields by changing the frequency. On the other hand, the product ratio of mono-trifluoromethylated compound **B** increased with increasing frequency, reaching a local maximum at 10^0 Hz (a period of 0.1 sec on time and 0.9 sec off time) and then reaching a maximum at 10^5 Hz. The formation of bis-trifluoromethylated compounds **C** and **D** is suppressed in the low frequency range ($\sim 10^{-2}$ Hz), although the yields of **C** and **D** at high frequency range varied slightly, remaining at around 6% and 2%, respectively. In this way, we showed that frequency which is one of the optical parameters, has a great influence on the efficiency and selectivity of the reaction, even though the total light intensity and the total irradiation time are the same, that is, the total number of photons is the same. Furthermore, by questing the origin of the effect of frequency, it is expected to construct a new photochemical reaction with frequency as a parameter. We are currently investigating the details of the effect of frequency on this reaction.

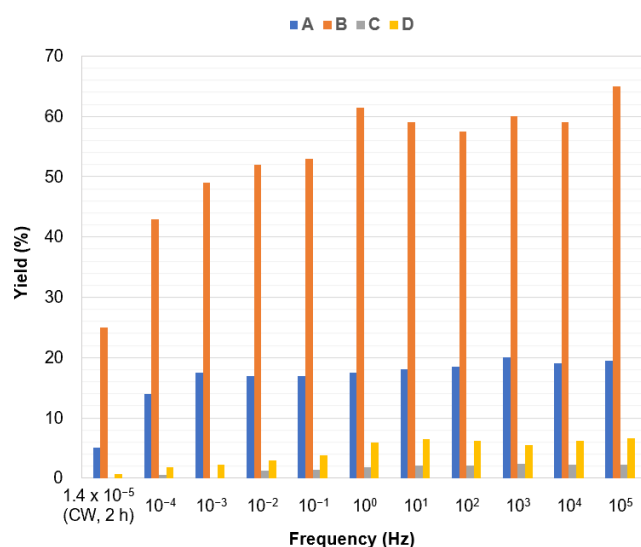


Fig. 2 Variation of yield and production ratio of mono-trifluoromethylated compounds **A** and **B** and bis-trifluoromethylated compounds **C** and **D** at different frequencies.

Conclusion

In conclusion, we have demonstrated for the first-time pulsed light-induced trifluoromethylation reaction with simple reaction condition by treating frequencies of pulsed light source as an item for evaluation of the reaction conditions. We also found the pulsed light irradiation improved the yield and regioselectivity of the reaction and by changing parameters of light source could be important item for controlling the reaction itself. An effect of frequency, that means ON/OFF time ratio for this reaction might be considered that it related to lifetime of active species and concentration of photocatalyst or reaction intermediates. Elucidation of the effectiveness of frequency is expected to establish new methods for reaction control and will contribute to develop new reactions.

Acknowledgment

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Conflicts of interest

The authors declare no conflicts of interest.

References

- 1 (a) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (b) R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, *Chem. Soc. Rev.*, 2011, **40**, 3496; (c) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315; (d) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422; (e) X. Gao, Y.-L. Xiao, X. Wan and X. Zhang, *Angew. Chem., Int. Ed.*, 2018, **57**, 3187; (f) J. Han, L. Kiss, H. Mei, A. M. Remete, M. P.-Svet, D. M. Sedgwick, R. Roman, S. Fustero, H. Moriwaki and V. A. Soloshonok, *Chem. Rev.*, 2021, **121**, 4678.
- 2 (a) W. Zhu, J. Wang, S. Wang, Z. Gu, J. L. Aceña, K. Izawa, H. Liu and V. A. Soloshonok, *J. Fluorine Chem.*, 2014, **167**, 37; (b) M. A. Miller and E. M. Sletten, *ChemBioChem*, 2020, **21**, 3451; (c) A. Abula, Z. Xu, Z. Zhu, C. Peng, Z. Chen, W. Zhu and H. A. Aisa, *J. Chem. Inf. Model.*, 2020, **60**, 6242; (d) A. S. Nair, A. K. Singh, A. Kumar, S. Kumar, S. Sukumaran, V. P. Koyiparambath, L. K. Pappachen, T. M. Rangarajan, H. Kim and B. Mathew, *Processes*, 2022, **10**, 2054.
- 3 (a) T. Koike and M. Akita, *Top Catal.*, 2014, **57**, 967; (b) X. Pan, H. Xia and J. Wu, *Org. Chem. Front.*, 2016, **3**, 1163; (c) E. H. Oh, H. J. Kim and S. B. Han, *Synthesis*, 2018, **50**, 3346; (d) T. Koike, *Asian J. Org. Chem.*, 2020, **9**, 529; (e) C. H. Ka, S. Kim and E. J. Cho, *Chem. Rec.*, 2023, e202300036.
- 4 D. A. Nagib and D. W. C. MacMillan, *Nature*, 2011, **480**, 224.
- 5 T. D. Svejstrup, A. Chatterjee, D. Schekin, T. Wagner, J. Zach, M. J. Johansson, G. Bergonzini and B. König, *ChemPhotoChem*, 2021, **5**, 808.
- 6 (a) E. Olvera-Gonzalez, D. Alaniz-Lumbreras, R. Ivanov-Tsonchev, J. Villa-Hernández, C. Olvera-Olvera, E. González-Ramírez, M. Araiza-Esquivel, V. Torres-Argüelles and V. Castaño, *Comput. Electron. Agric.*, 2013, **92**, 48; (b) E. Olvera-Gonzalez, D. Alaniz-Lumbreras, V. Torres-Argüelles, E. González-Ramírez, J. Villa-Hernández, M. Araiza-Esquivel, R. Ivanov-Tsonchev, C. Olvera-Olvera and V. M. Castaño, *Light. Res. Technol.*, 2013, **46**, 128; (c) K.-H. Son, Y.-M. Jeon and M.-M. Oh, *Hortic. Environ. Biotechnol.*, 2016, **57**, 560; (d) P. S. C. Schulze, R. Guerra, H. Pereira, L. M. Schüler and J. C. S. Varela, *Trends Biotechnol.*, 2017, **35**, 1088; (e) O. D. Palmitessa, M. A. Pantaleo and P. Santamaria, *Agronomy*, 2021, **11**, 835; (f) E. Olvera-Gonzalez, N. Escalante-Garcia, D. Myers, P. Ampim, E. Obeng, D. Alaniz-Lumbreras and V. Castaño, *Energies*, 2021, **14**, 1603.
- 7 (a) C. K. Rokhsar, S. Lee and R. E. Fitzpatrick, *Dermatol. Surg.*, 2005, **31**, 1166; (b) J. D. Peterson and M. P. Goldman, *Dermatol. Surg.*, 2011, **37**, 555; (c) S. Karrer, E. Koh, K. Feise, D. H.-Wegener, S. Lischner, W. P.-Dormston, M. Podda, W. Prager, T. Walker and R.-M. Szeimies, *J. Dtsch. Dermatol. Ges.*, 2012, **11**, 137; (d) A. F. S. Sales, I. L. Pandolfo, M. de A. Cruz, J. R. Parisi, L. A. Garcia, C. C. S. Martignago, A. C. M. Renno and P. G. Vassão, *Arch. Dermatol. Res.*, 2022, **314**, 823.
- 8 (a) V. M. Gómez-López, P. Ragaert, J. Debevere and F. Devlieghere, *Trends Food Sci. Technol.*, 2007, **18**, 464; (b) N. Elmnasser, S. Guillou, F. Leroi, N. Orange, A. Bakhrouf and M. Federighi, *Can. J. Microbiol.*, 2007, **53**, 813; (c) G. Oms-Oliu, O. Martín-Belloso and R. Soliva-Fortuny, *Food Bioprocess Technol.*, 2010, **3**, 13; (d) J. Abida, B. Rayees and F. A. Masoodi, *Int. Food Research J.*, 2014, **21**, 839; (e) B. Kramer, J. Wunderlich and P. Muranyi, *J. Appl. Microbiol.*, 2017, **122**, 830; (f) R. Mandal, X. Mohammadi, A. Wiktor, A. Singh and A. P. Singh, *Appl. Sci.*, 2020, **10**, 3606.
- 9 H. Yokoi, T. Nakano, W. Fujita, K. Ishiguro and Y. Sawaki, *J. Am. Chem. Soc.*, 1998, **120**, 12453.
- 10 H. Yokoi, S. Moriizumi, K. Ishiguro and Y. Sawaki, *J. Photochem. Photobiol. A*, 1999, **125**, 39.
- 11 T. P. Nicholls, J. C. Robertson, M. G. Gardiner and A. C. Bissember, *Chem. Commun.*, 2018, **54**, 4589.
- 12 L. Cui, Y. Matusaki, N. Tada, T. Miura, B. Uno and A. Itoh, *Adv. Synth. Catal.*, 2013, **355**, 2203.