



Microflow photo-radical chlorination of cycloalkanes

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ABSTRACT

Photo-initiated radical chlorination of cycloalkanes was investigated using microflow reactors. Under natural light, microflow chlorination of cyclohexane with molecular chlorine proceeded well to give chlorocyclohexane with high selectivity for single-chlorination. Single-chlorination reaction of cycloalkanes with sulfuryl chloride can also be successfully carried out using a microflow reactor under irradiation using a 15 W black light.

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1. Introduction

The recent rapid progress of microflow reaction technology led synthetic organic chemists to examine a variety of organic reactions using microreactors [1,2]. Since microflow reactors provide high heat and mass transfer rate for organic reactions, those reactions which are difficult to control using conventional batch equipments can be a potential target for the improvement. Work in our laboratories has been directed toward the design and application of microflow reaction technologies to conventional organic synthesis [3] and to the end, we previously reported on effective continuous microflow reactions, which include Pd-catalyzed coupling reactions in ionic liquids [4], thermally induced radical reactions [5] and photo-irradiation reactions [6]. Photoreactions using microreactors have promise to use light energy at minimum because the light penetration is ideal inherent to the thinness of the microreactor and the resultant short residence time even allows the avoidance of undesirable second reactions [7,8]. As such an application of photo-irradiation reactions, we recently reported on a successful multi-gram-scale production of a steroidal compound by the Barton reaction using a microflow reactor in combination with an energy saving light source such as black light [9]. We also achieved diastereoselective [2+2] photoaddition reactions using a microflow system [10].

As part of our ongoing interest in organic synthesis by microflow photo-irradiation technologies, we began to investigate radical chlorination of alkanes using a microreactor under photo-

irradiation conditions. Radical chlorination of alkanes is one of the most basic organic reactions, and studies on this reaction continue for more than half century [11–13]. While various reagents including molecular chlorine [11] and sulfuryl chloride [12] are used for radical chlorination of alkanes with variable selectivity [14], in order to achieve reproducible selectivity for single chlorination over competing polychlorination, strict control of molar ratios, light power, and reaction time are required for batch systems. We thought that radical chlorination in a microflow system would be useful even for alkane chlorination in terms of controlled selectivity, efficiency with energy saving light sources. Although radical chlorination using a microflow system was previously reported for chlorination of a benzylic position [15–17], no work on chlorination of simple alkanes using a microreactor has been reported; we report herein radical chlorination of cyclic alkanes using sulfuryl chloride and molecular chlorine can be effectively carried out using a continuous microflow system and visible lights.

2. Experimental

2.1. General information

GC analysis was performed with a SHIMADZU GC-18A; column: J&W DB-1 (i.d.: 0.32 mm, length: 30 m, film: 1 μm), N₂ (700 kPa); temperature program: 60 °C for 6 min, then 60–250 °C at 20 °C/min. GC yields were determined by comparing the peak area with that of the standard solution containing an authentic sample. All products in this study are known and commercially available; their spectral data are in agreement with the authentic samples.

Microflow chlorinations were carried out using a DNS F005D03-HB (1000 μm width, 300 μm depth and 2.35 m length, and total

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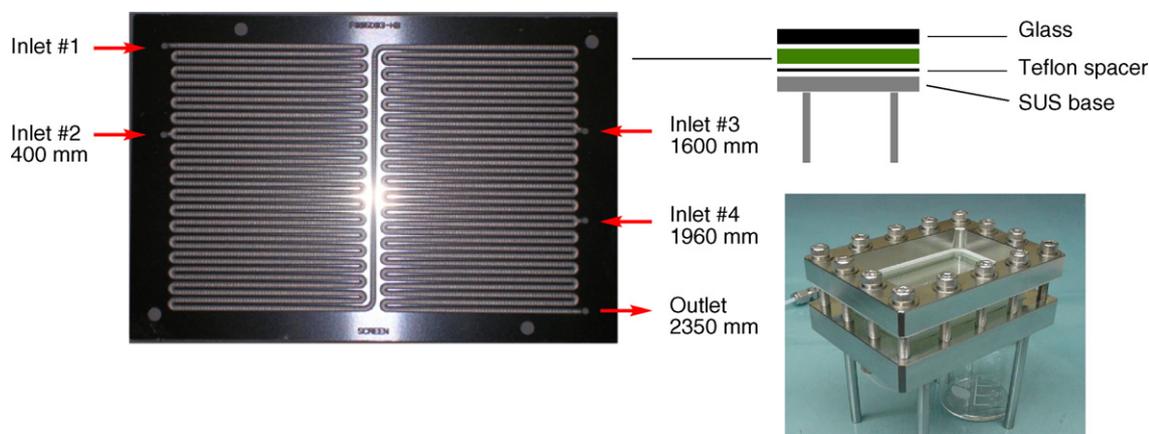


Fig. 1. DNS microreactor F005D03-HB.

hold-up volume: 0.7 mL, by Dainippon Screen Mfg. Co., Ltd., Japan) under natural light or a Mikrogas Dwell Device (1000 μm width, 500 μm depth and 1.9 m length, and total hold-up volume: 0.95 mL, by Mikrogas Chemtech GmbH, Germany) attached with a 15 W black lights. Inline check valve (6.9 MPa, CV-3000, GL-Sciences Inc., Japan) was used for the chlorination reaction with molecular chlorine.

2.2. Procedure for a continuous microflow chlorination of cyclohexane with molecular chlorine

The continuous microflow system was comprised of a T-shaped micromixer (i.d. = 500 μm) and the DNS reactor, two gas/liquid feed stainless tube and an outlet. A 10 mL gas tight syringe containing cyclohexane (5 mL, 46 mmol) was attached to an inlet of the

micromixer and a 25 mL gas tight syringe containing molecular chlorine (25 mL, 1.1 mmol) was connected to the other inlet of the micromixer through a check valve. The syringes were pumped using syringe pumps at flow rates of 1.32 mL/h and 7.68 mL/h for cyclohexane and molecular chlorine, respectively (residence time: 19 min). The mixture of product eluted from the outlet was collected in a flask containing 10% sodium sulfite. Yield of chlorocyclohexane was determined by GC analysis.

2.3. General procedure for a continuous microflow chlorination of cycloalkane with sulfonyl chloride

A 10 mL gas tight syringe containing a mixture of sulfonyl chloride (283 mg, 2.1 mmol) in cyclohexane (6.73 g, 80.0 mmol) was attached to the inlet of the Mikrogas device. The syringe was

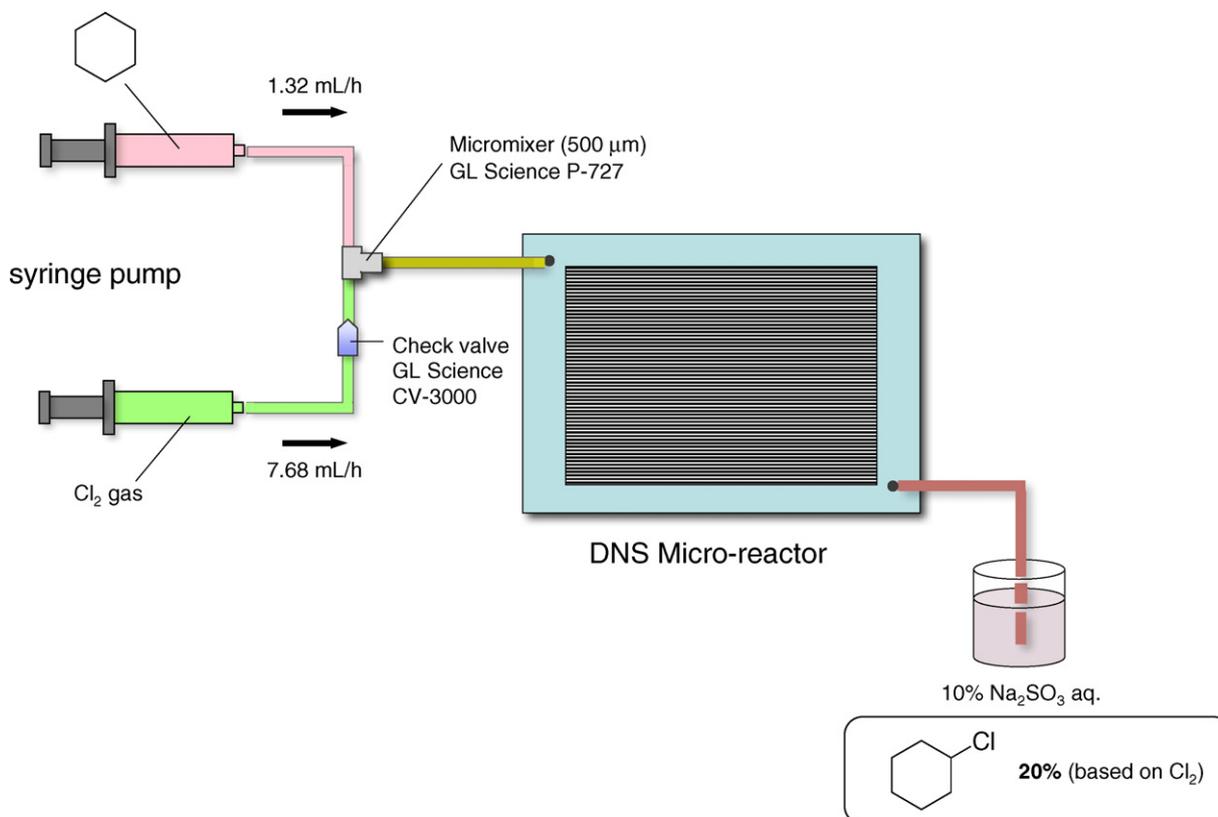


Fig. 2. Microflow chlorination with molecular chlorine.

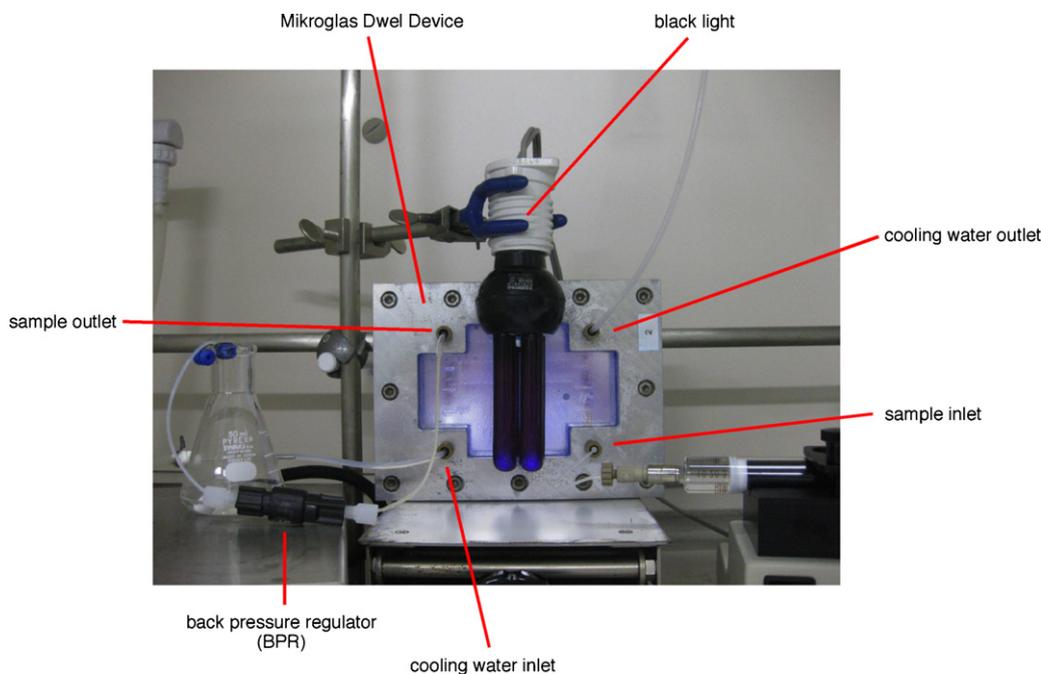


Fig. 3. Devices for microflow chlorination using sulfuryl chloride.

pumped using syringe pumps at flow rates of 1 mL/h or 3 mL/h (residence time: 57 min or 19 min) under photo irradiation using a 15 W of black light. The microreactor was cooled with water during the reaction. A mixture eluted from the outlet was collected in a flask containing 10% sodium sulfite. Yield of chlorocyclohexane was determined by GC analysis.

3. Results and discussion

3.1. Microflow chlorination of cyclohexane with molecular chlorine and room light

We started our chlorination study using a microflow system with cyclohexane as the substrate. We chose a DNS microreactor F005D03-HB composed of photo-etched stain-less steel microchannels with covered Pyrex glass (Fig. 1, 1000 μm width, 300 μm depth and 2.35 m length, and total hold-up volume: 0.7 mL)

for this reaction. The total figure of the flow reaction system is shown in Fig. 2. Thus, the DNS microreactor was connected with a T-shaped micromixer (i.d. = 500 μm), and a check valve (6.9 MPa) was fitted to one of the inlets of the micromixer for avoiding backward flow of chlorine. As molecular chlorine is known to react with alkanes violently under UV irradiation, we used natural room light as the light source. Thus, we carried out chlorination of cyclohexane with molecular chlorine at room temperature in natural light with residence time of 19 min (measured value). As we envisioned the reaction gave chlorocyclohexane with nearly complete selectivity for single chlorination product (>95%) in the yield of 20%.

3.2. Microflow chlorination with sulfuryl chloride and black light

We then examined chlorination using sulfuryl chloride as a chlorination reagent. As sulfuryl chloride is known to react more gently than molecular chlorine, a 15 W black light (peak wavelength:

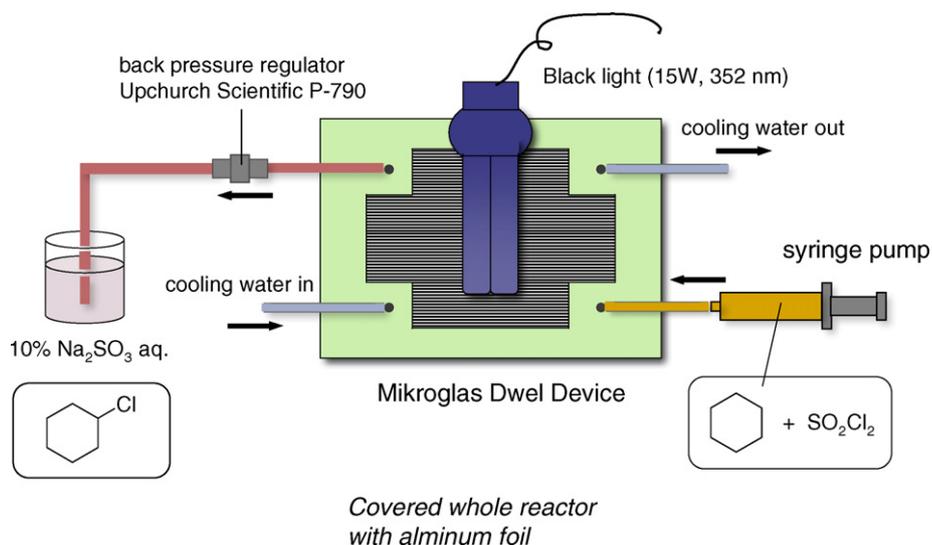
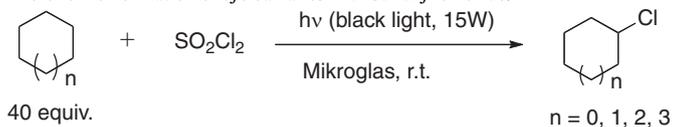


Fig. 4. Microflow chlorination with sulfuryl chloride.

Table 1
Microflow chlorination of cycloalkanes with sulfuryl chloride.^a



Entry	Substrate	Flow rate (mL/h)	Residence time (min)	Yield of chlorocycloalkane (%) ^b
1		3.0	19	22
2 ^c		3.0	19	20
3		1.0	57	35
4 ^d		1.0	57	37
5 ^e		1.0	57	45
6		3.0	19	41
7		1.0	57	61
8		1.0	57	87
9		1.0	57	47

^a Reaction conditions: Mikroglas Dwell Device, cycloalkane (80 mmol), sulfuryl chloride (2.1 mmol), and 15 W black light, r.t.

^b GC yield.

^c Cyclohexane 80 equiv.

^d Using a back pressure regulator.

^e Using a back pressure regulator and two black lights.

352 nm) was employed for this reaction, in which a Mikroglas Dwell Device (Foturan glass, 1000 μm width, 500 μm depth and 1.9 m length, and total hold-up volume: 0.95 mL) was used as a microreactor. The total system for this reaction is shown in Figs. 3 and 4 and the results are summarized in Table 1. When a solution containing sulfuryl chloride and 40 molar equivalents of cyclohexane was introduced to a microreactor with a residence time 19 min (measured value, flow rate: 3.0 mL/h) at room temperature, the reaction gave chlorocyclohexane selectively in 22% yield (entry 1). While increasing molar ratio of cyclohexane to 80 equiv. did not affect the yield of the product (20%, entry 2), extending residence time (57 min, flow rate: 1.0 mL/h) raised product yield to 35% (entry 3). As shown in Fig. 5, plug flow was observed due to gases of SO_2 and HCl generated during the reaction. To avoid occasional disturbance by the plug flow in the microreactor, a back pressure regulator (BPR: Upchurch Scientific, P-790, 0.3 bar) was fitted, resulting in the effective suppression of the plug flow (Fig. 6). The reaction using two black lights resulted in slightly better yield of the product (entry 5).

Microflow chlorinations of cyclopentane, cycloheptane and cyclooctane were also carried out (entries 6–9). Again, decrease in the yield was observed using faster flow rate for the case of cyclopentane (entry 6). Under the employed conditions all chlo-



Fig. 5. Without BPR (plug flow).

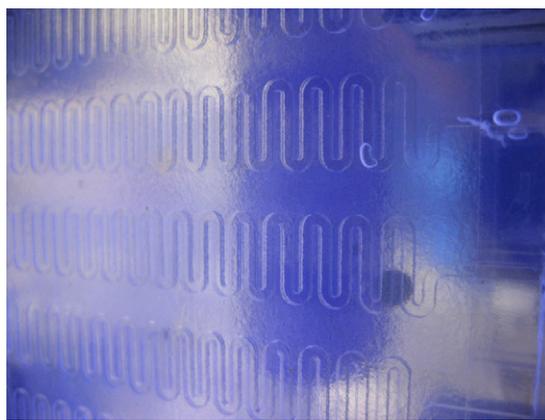


Fig. 6. With BPR (plug flow suppressed).

ration reactions proceeded well to give monochlorocycloalkanes with high selectivity (>95%) [18].

4. Conclusions

In summary, we have demonstrated that radical chlorination reaction of cycloalkanes with molecular chlorine and sulfuryl chloride using a microflow reactor proceeded well under photoirradiation conditions (natural light and black light) to give chlorocycloalkanes with high selectivity for single chlorination. In the reaction using sulfuryl chloride, plug flow inherent to the gas evolution was effectively suppressed by the use of a back-pressure regulator.

Acknowledgements

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References

- For recent reviews, see;
 - K. Geyer, T. Gustafsson, P.H. Seeberger, *Synlett* (2009) 2382–2391;
 - J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* 14 (2008) 7450–7459;
 - B.K. Singh, N. Kaval, S. Tomar, E. Van der Eycken, V.S. Parmar, *Org. Process Res. Dev.* 12 (2008) 468–474;
 - P. Watts, C. Wiles, *Org. Biomol. Chem.* 5 (2007) 727–732;
 - B. Ahmed-Omer, J.C. Brandt, T. Wirth, *Org. Biomol. Chem.* 5 (2007) 733–740;
 - K. Geyer, J.D.C. Codée, P.H. Seeberger, *Chem. Eur. J.* 12 (2006) 8434–8442;
 - T. Wirth (Ed.), *Microreactors in Organic Synthesis and Catalysis*, Wiley-VCH, Weinheim, 2008.
- For recent work on organic synthesis using microreactors, see;
 - M.W. Bedore, N. Zaborenko, K.F. Jensen, T.F. Jamison, *Org. Process Res. Dev.* 14 (2010) 432–440;

- (b) A. Herath, R. Dahl, N.D.P. Cosford, *Org. Lett.* 12 (2010) 412–415;
(c) M. Damm, T.N. Glasnov, C.O. Kappe, *Org. Process Res. Dev.* 14 (2010) 215–224;
(d) A.R. Bogdan, S.L. Poe, D.C. Kubis, S.J. Broadwater, D.T. McQuade, *Angew. Chem. Int. Ed.* 48 (2009) 8547–8550;
(e) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem. Int. Ed.* 48 (2009) 8063–8065;
(f) J. Jin, M. Cai, J. Li, *Synlett* (2009) 2534–2538;
(g) L. Kong, Q. Lin, X. Lv, Y. Yang, Y. Jia, Y. Zhou, *Green Chem.* 11 (2009) 1108–1111;
(h) A. Nagaki, E. Takizawa, J. Yoshida, *Chem. Lett.* 38 (2009) 486–487;
(i) B. Ahmed-Omer, D.A. Barrow, T. Wirth, *Tetrahedron Lett.* 50 (2009) 3352–3355;
(j) Y. Lan, M. Zhang, W. Zhang, L. Yang, *Chem. Eur. J.* 15 (2009) 3670–3673;
(k) A. Odedra, P.H. Seeberger, *Angew. Chem. Int. Ed.* 48 (2009) 2699–2702;
(l) C.B. McPake, C.B. Murray, G. Sandford, *Tetrahedron Lett.* 50 (2009) 1674–1676;
(m) M. Baumann, I.R. Baxendale, S.V. Ley, *Synlett* (2008) 2111–2114.
- [3] For a review on our work, see T. Fukuyama, M.T. Rahman, M. Sato, I. Ryu, *Synlett* (2008) 151–163.
- [4] For our recent work on Pd-catalyzed coupling reactions using a microreactor, see;
(a) T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato, I. Ryu, *Org. Lett.* 4 (2002) 1691–1694;
(b) S. Liu, T. Fukuyama, M. Sato, I. Ryu, *Org. Process Res. Dev.* 8 (2004) 477–481;
(c) M.T. Rahman, T. Fukuyama, N. Kamata, M. Sato, I. Ryu, *Chem. Commun.* (2006) 2236–2238.
- [5] T. Fukuyama, M. Kobayashi, M.T. Rahman, N. Kamata, I. Ryu, *Org. Lett.* 10 (2008) 533–536.
- [6] T. Fukuyama, Y. Hino, N. Kamata, I. Ryu, *Chem. Lett.* 33 (2004) 1430–1431.
- [7] For reviews on photo-reactions using a microreactor, see;
(a) Y. Matsushita, T. Ichimura, N. Ohba, S. Kumada, K. Sakeda, T. Suzuki, H. Tanibata, T. Murata, *Pure Appl. Chem.* 79 (2007) 1959–1968;
(b) E.E. Coyle, M. Oelgemöller, *Photochem. Photobiol. Sci.* 7 (2008) 1313–1322.
- [8] For recent work on photoreactions using microreactors, see;
(a) Y. Matsushita, M. Iwasawa, T. Suzuki, T. Ichimura, *Chem. Lett.* 38 (2009) 846–847;
(b) A. Ouchi, H. Sakai, T. Oishi, M. Kaneda, T. Suzuki, A. Saruwatari, T. Obata, *J. Photochem. Photobiol. A* 199 (2008) 261–266;
(c) Y. Matsushita, N. Ohba, T. Suzuki, T. Ichimura, *Catal. Today* 132 (2008) 153–158;
(d) H. Mukae, H. Maeda, S. Nashihara, K. Mizuno, *Bull. Chem. Soc. Jpn.* 80 (2007) 1157–1161;
(e) H. Maeda, H. Mukae, K. Mizuno, *Chem. Lett.* 34 (2005) 66–67.
- [9] (a) A. Sugimoto, Y. Sumino, M. Takagi, T. Fukuyama, I. Ryu, *Tetrahedron Lett.* 47 (2006) 6197–6200;
(b) A. Sugimoto, T. Fukuyama, Y. Sumino, M. Takagi, I. Ryu, *Tetrahedron* 65 (2009) 1593–1598.
- [10] K. Tsutsumi, K. Terao, H. Yamaguchi, S. Yoshimura, T. Morimoto, K. Kakiuchi, T. Fukuyama, I. Ryu, *Chem. Lett.* 39 (2010) 828–829.
- [11] For chlorination of alkanes with molecular chlorine;
(a) K.U. Ingold, J. Luszyk, K.D. Raner, *Acc. Chem. Res.* 23 (1990) 219–225, and references cited in it;
(b) B. Fletcher, N.K. Suleman, J.M. Tanko, *J. Am. Chem. Soc.* 120 (1998) 11839–11844;
(c) N. Sun, K.J. Klabunde, *J. Am. Chem. Soc.* 121 (1999) 5587–5588.
- [12] For radical chlorination of alkanes with sulfuryl chloride;
(a) M.S. Kharasch, H.C. Brown, A.B. Ash, *J. Am. Chem. Soc.* 61 (1939) 2142–2150;
(b) H.C. Brown, A.B. Asii, *J. Am. Chem. Soc.* 77 (1955) 4019–4024;
(c) G.A. Russell, H.C. Brown, *J. Am. Chem. Soc.* 77 (1955) 4031–4035;
(d) I. Tabushi, Z. Yoshida, Y. Tamaru, *Tetrahedron* 29 (1973) 81–84;
(e) A.F. Andrews, C. Glidewell, J.C. Walton, *J. Chem. Res. Synopses* (1978) 294;
(f) A.S. Dneprovskii, E.V. Eliseenkov, S.A. Mil'tsov, *Z. Org. Khim.* 16 (1980) 1086–1087;
(g) V. Khanna, P. Tamilselvan, S.J.S. Kalra, J. Iqbal, *Tetrahedron Lett.* 35 (1994) 5935–5938.
- [13] For radical chlorination of alkanes using other than sulfuryl chloride and molecular chlorine, see;
(a) J.L. Brokenshire, A. Nechvatal, J.M. Tedder, *Trans. Faraday Soc.* 66 (1970) 2029–2037;
(b) J.M. Krasniewski Jr., M.W. Mosher, *J. Org. Chem.* 39 (1974) 1303–1306;
(c) G.A. Olah, P. Schilling, R. Renner, I. Kerekes, *J. Org. Chem.* 39 (1974) 3472–3478;
(d) R.A. Johnson, F.D. Greene, *J. Org. Chem.* 40 (1975) 2192–2196;
(e) M.W. Mosher, G.W. Estes, *J. Am. Chem. Soc.* 99 (1977) 6928–6932;
(f) N.C. Deno, E.J. Gladfelder, D.G. Pohl, *J. Org. Chem.* 44 (1979) 3728–3729;
(g) A. Arase, M. Hoshi, Y. Masuda, *Chem. Lett.* (1979) 961–964;
(h) M.W. Mosher, G.W. Estes, *J. Org. Chem.* 47 (1982) 1875–1879;
(i) R. Nouguier, J.M. Surzur, A. Virgili, *Anal. Quim. Ser. C: Quim. Org. Bioquim.* 78 (1982) 261–262;
(j) M. Hoshi, Y. Masuda, A. Arase, *Chem. Lett.* (1984) 195–198;
(k) R. Davis, J.L.A. Durrant, C.C. Rowland, *Organomet. Chem.* 316 (1986) 147–162.
- [14] M.B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 6th ed., Wiley, New Jersey, 2007, pp. 954–955.
- [15] H. Ehrlich, D. Linke, K. Morgenschweis, M. Baerns, K. Jahnisch, *Chimia* 56 (2002) 647–653.
- [16] For a review of halogenations using a microreactor, see P. Löb, H. Löwe, V. Hessel, *J. Fluorine Chem.* 125 (2004) 1677–1694.
- [17] For recent papers on fluorination using a microreactor, see;
(a) G. Sandford, *J. Fluorine Chem.* 128 (2007) 90–104;
(b) M. Baumann, I.R. Baxendale, S.V. Ley, *Synlett* (2008) 2111–2114;
(c) K. Geyer, T. Gustafsson, P.H. Seeberger, *Synlett* (2009) 2382–2391;
(d) N. de Mas, A. Günther, M.A. Schmidt, K.F. Jensen, *Ind. Eng. Chem. Res.* 48 (2009) 1428–1434;
(e) M. Baumann, I.R. Baxendale, L.J. Martin, S.V. Ley, *Tetrahedron* 65 (2009) 6611–6625;
(f) T. Gustafsson, R. Gilmour, P.H. Seeberger, *Chem. Commun.* (2008) 3022–3024.
- [18] Taking sensitivity limit of detection by GC, we used rough number >95%. Only small amount of dichlorides was detected by GC and GC–MS.