Koch–Haaf reaction of adamantanol in an acid-tolerant hastelloy-made microreactor

Takahide Fukuyama*, Yu Mukai and Ilhyong Ryu*
highly exothermic, the reaction is typically carried out at controlled temperature by means of a cooling bath, such as an ice bath, and with carefully controlled slow addition of reagents through an addition funnel. The temperature control causes a serious problem especially for large scale synthesis. Herein, we report that the Koch–Haaf reaction in a microflow reactor can be carried out at room temperature without any cooling equipment. The employed hastelloy-made microreactor system was compatible with corrosive (strongly acidic) conditions and confirmed for gram scale (7.1 g) synthesis of 1-adamantanecarboxylic acid in ca. 1 h operation.

Results and Discussion

The carbonylation reaction of 1-adamantanol (1a) was investigated in a microflow system as a model reaction. Since the Koch–Haaf reaction requires the use of concentrated sulfuric acid, an acid-tolerant system is essential. For this study, we employed a combination of a hastelloy-made micromixer (MiChS, β-150H) having 150 μm reactant inlet holes and 200 μm × 300 μm channels (Figure 1), and a PTFE tube (1.0 mm i.d. × 3 m, inner volume: 2.36 mL) as a residence time unit. To this reactor system, a hastelloy-made microextraction unit (a flow-workup system) was attached (Figure 2 and Figure 3). The microextraction unit has three inlets and one outlet (channel size: 1 mm i.d. × 14 cm). The reaction mixture was mixed at T-shaped junctions with Et_2O and water, and a biphasic mixture was collected from the outlet.

1-Adamantanol (1a) dissolved in HCOOH (flow rate: 0.30 mL/min) and 98% H_2SO_4 (flow rate: 0.88 mL/min) were mixed in the micromixer at room temperature, and the resulting reaction mixture was fed into the PTFE tube and then into the extraction unit, in which Et_2O (flow rate: 2.5 mL/min) and water (2 mL/min) were introduced to extract the carbonylation product and remove excess acids (Scheme 1). The biphasic mixture was collected in a flask and the ether layer was concentrated in vacuo. 1-Adamantanecarboxylic acid (2a) was obtained in 89% isolated yield after purification by silica gel column chromatography. While the residence time was a priori expected to be 2 min based on the total flow rate of the reagents and inner volume of the residence time unit, the observed
Scheme 1: Synthesis of 1-adamantanecarboxylic acid (2a) in a microflow system.

residence time was 1.5 min due to a plug flow by the CO gas generated.

For comparison, we also carried out the batch reaction in a 50 mL glass flask on 4 mmol scale to give 2a in 92% yield. In the batch reaction, the careful addition of a solution of 1a in formic acid over a period of 5 min and cooling in an ice bath were necessary to achieve good results. Indeed, without a cooling bath, we observed that the temperature of the reaction mixture rose up to 50–60 °C. It is therefore remarkable that the reaction in the microflow system can be performed successfully at room temperature without any cooling unit.

We then investigated the reaction of some other adamantanol derivatives, such as that of 2-adamantanol (1b) and 2-methyl-2-adamantanol (1c) (Scheme 2). The reaction of 1b in a microflow system gave a mixture of 2-adamantanecarboxylic acid (2b) and 1-adamantanecarboxylic acid (2a) (82% total yield, 2b:2a = 58:42), in which the latter compound originated from the isomerized tertiary cation, which derived from the initially formed secondary cation. The batch reaction gave a mixture of 2b and 2a in 65% total yield with a greater proportion of the rearranged product (2b:2a = 14:86). The reaction of 2-methyl-2-adamantanol (1c) resulted in a mixture of the carboxylated products, 2c, 2c’, and 2c” in 97% total yield (2c:2c’:2c” = 23:53:24). The batch reaction resulted in an inferior yield with more of the rearranged products (83% yield, 2c:2c’:2c” = 19:62:19). All results are summarized in Table 1.

Multigram scale synthesis of 2a from 1a was carried out in a continuous flow reaction. When the reaction of 1a (45 mmol) was performed for 55 min, 7.1 g of 2a was obtained in 88% yield, demonstrating that the present microflow system can be used for multigram scale synthesis without any problems (Scheme 3).

Conclusion
In this work, we demonstrated that the Koch–Haaf reaction of adamantanol was successfully carried out in an acid-tolerant microflow system comprising a hastelloy-made micromixer, a PTFE tube, and a hastelloy-made microextraction unit. Unlike in the batch system, the reaction could be carried out at room temperature without any cooling equipment. The employed reaction-to-workup system was useful for the multigram scale
Table 1: Koch–Haaf reactions of adamantanol.a

| Entry | 1  | Reactor | Conditions | Product (yield)b |
|-------|----|---------|------------|-----------------|
| 1     | 1a | microflow | T: 20 °C  
flow rate (1a/HCO2H): 0.30 mL/min  
flow rate (H2SO4): 0.88 mL/min  
residence time: 2 min\(^c\)  
residence time: 1.5 min\(^d\) | ![COOH] 2a 89% |
| 2     | 1a | batch | T: 15–20 °C  
addition time: 5 min  
reaction time: 2 min | ![COOH] 2a 92% |
| 3     | 1b | microflow | T: 20 °C  
flow rate (1b/HCO2H): 0.30 mL/min  
flow rate (H2SO4): 0.88 mL/min  
residence time: 2 min\(^c\)  
residence time: 1 min\(^d\) | ![COOH] 2b 82% (58:42)  
![COOH] 2a | ![COOH] 2a |
| 4     | 1b | batch | T: 17–20 °C  
addition time 5 min  
reaction time 1 min | ![COOH] 2b 65% (14:86)  
![COOH] 2a |
| 5     | 1c | microflow | T: 20 °C  
flow rate (1c/HCO2H): 0.01 mL/min  
flow rate (H2SO4): 0.3 mL/min  
residence time: 20 min\(^c\)  
residence time: 2.5 min\(^d\) | ![COOH] 2c 97% (23:53:24)  
![HOOC] 2c\(^{*}\) (47:53) |
| 6     | 1c | batch | T: 17–20 °C  
addition time 3 min  
reaction time 10 min | ![COOH] 2c 83% (19:62:19)  
![HOOC] 2c\(^{*}\) (47:53) |

a\(^1\) (4 mmol), HCOOH (6 equiv), H2SO4 (20 equiv); bisolated yield after column chromatography on SiO\(_2\); ccalculated; dobserved.

synthesis of 1-adamantanecarboxylic acid (2a). We are now expanding the system to other cationic systems and the results will be published in due course.

**Experimental**

Typical procedure for Koch–Haaf reaction in a microflow system. Multigram scale synthesis of 1-adamantanecarboxylic acid (2a). 1-Adamantanol (1a, 60 mmol, 9.2 g) was dissolved in 96% HCOOH (360 mmol, 16.6 g), and the solution was placed in a 50 mL syringe (22.3 mL), which was then attached to a syringe pump. Concentrated H2SO4 (99%) (1.2 mol, 64 mL) was placed in 100 mL syringe. These liquids were mixed in the hastelloy micromixer (150 μm) (flow rate: 1a in HCOOH = 0.3 mL/min, H2SO4 = 0.88 mL/min). The resulting reaction mixture was then fed into the residence time unit (PTFE tube, 1 mm i.d. × 3 m). The residence time was observed to be 1.5 min. The mixture of products was fed into the hastelloy-made extraction unit, which was cooled by an ice/water bath. Et2O (2.5 mL/min) and water (2 mL/min) were fed into the extraction unit. The mixture that was eluted during the first 5 min was discarded and the portion that followed was collected for 55 min (1a: 45 mmol). The ethereal layer was separated, and washed with 1.4 N KOH aq. The aqueous layer was acidified with 1 N HCl and extracted with Et2O. The organic layer was dried over MgSO4, filtered, and evaporated. 1-Adamantanecarboxylic acid (2a) was obtained in 88% yield as a white solid (7.1 g, mp 171–172 °C). The obtained product was identified by comparison of the 1H NMR and 13C NMR spectra with those of commercially available authentic samples. All other products, 2b, 2c, 2c\(^\prime\), and 2c\(^{*}\) were identified by means of NMR spectroscopy by comparison with literature data [32,33].
Typical procedure for Koch–Haaf reaction in a batch reaction system

In a 50 mL two-necked round bottom flask, 99% H\textsubscript{2}SO\textsubscript{4} (80 mmol, 7.85 g) was placed. A solution of 1-adamantanol (1a, 4 mmol, 613 mg) in 96% HCOOH (24 mmol, 1.01 g) was added through a dropping funnel over a period of 5 min, while the temperature of the reaction mixture was maintained at 15–20 °C in an ice/water bath. The reaction mixture was stirred at 15–20 °C for an additional 2 min, poured into ice/water and extracted with Et\textsubscript{2}O. The ethereal layer was washed with 1.4 N KOH aq, and the aqueous layer was acidified with 1 N HCl and extracted with Et\textsubscript{2}O. The ethereal layer was washed with 1.4 N NaOH aq, and the aqueous layer was evaporated and purified by column chromatography on SiO\textsubscript{2}. Compound 2a was obtained in 92% yield (667 mg). The reaction of 1b and 1c was carried out by a similar procedure.

Acknowledgements

The authors thank MCPT and NEDO for financial support of this work. IR acknowledges the Grant-in-Aid for Scientific Research on Innovative Areas (No. 2105) from the MEXT Japan for funding.

References

1. Wirth, T., Ed. Microreactors in Organic Synthesis and Catalysis; Wiley-VCH: Weinheim, Germany, 2008. doi:10.1002/9783527622856
2. Hessel, V.; Renken, A.; Schouten, J. C.; Yoshida, J. Micro Process Engineering; Wiley-VCH: Weinheim, Germany, 2009.
3. Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. Chem. Rev. 2007, 107, 2300–2318. doi:10.1021/cr050944c
4. Yoshida, J.; Nagaki, A.; Yamada, T. Chem.–Eur. J. 2008, 14, 7450–7459. doi:10.1002/chem.200800582
5. Lin, W.-Y.; Wang, Y.; Wang, S.; Tseng, H.-R. Nano Today 2009, 4, 470–481. doi:10.1016/j.nantod.2009.10.007
6. McMullen, J. P.; Jensen, K. F. Annu. Rev. Anal. Chem. 2010, 3, 19–42. doi:10.1146/annurev.anchem.111808.073718
7. Webb, D.; Jamison, T. F. Chem. Sci. 2010, 1, 675–680. doi:10.1039/C0CS00381F
8. Yoshida, J. Chem. Rec. 2010, 10, 332–341. doi:10.1007/bf03380020
9. Wegner, J.; Ceylan, S.; Kirschning, A. Chem. Commun. 2011, 47, 4583–4592. doi:10.1039/c005060a
10. Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. Synlett 2008, 151–163. doi:10.1055/s-2007-1000884
11. Fukuyama, T.; Shinnmen, M.; Nishitani, S.; Sato, M.; Ryu, I. Org. Lett. 2002, 4, 1691–1694. doi:10.1021/ol0257732
12. Liu, S.; Fukuyama, T.; Sato, M.; Ryu, I. Org. Process Res. Dev. 2004, 8, 477–481. doi:10.1021/op040320h
13. Rahman, M. T.; Fukuyama, T.; Kamata, N.; Sato, M.; Ryu, I. Chem. Commun. 2006, 2236–2238. doi:10.1039/B60970K
14. Fukuyama, T.; Kobayashi, M.; Rahman, M. T.; Kamata, N.; Ryu, I. Org. Lett. 2008, 10, 533–536. doi:10.1021/ol802778z
15. Wieshöfer, I. C.; Studer, A.; Rahman, M. T.; Fukuyama, T.; Ryu, I. Org. Lett. 2009, 11, 2457–2460. doi:10.1021/ol900713d
16. Fukuyama, T.; Rahman, M. T.; Kamata, N.; Ryu, I. Beilstein J. Org. Chem. 2009, 5, No. 34. doi:10.3762/bjoc.5.34
17. Fukuyama, T.; Hino, Y.; Kamata, N.; Ryu, I. Chem. Lett. 2004, 33, 1430–1431. doi:10.1246/cl.2004.1430
18. Sugimoto, A.; Sumino, Y.; Takagi, M.; Fukuyama, T.; Ryu, I. Tetrahedron Lett. 2006, 47, 6197–6200. doi:10.1016/j.tetlet.2006.06.153
19. Sugimoto, A.; Fukuyama, T.; Sumino, Y.; Takagi, M.; Ryu, I. Tetrahedron 2009, 65, 1593–1598. doi:10.1016/j.tet.2008.12.063
20. Matsubara, H.; Hino, Y.; Tokizane, M.; Ryu, I. Chem. Eng. J. 2011, 167, 567–571. doi:10.1016/j.cej.2010.08.086
21. Tsutsui, K.; Terao, K.; Yamaguchi, H.; Yoshimura, S.; Morimoto, T.; Kakuchi, K.; Fukuyama, T.; Ryu, I. Chem. Lett. 2010, 39, 828–829. doi:10.1246/cl.10.828
22. Suga, S.; Nagaki, A.; Yoshida, J. Chem. Commun. 2003, 354–355. doi:10.1039/B211433J
23. For Friedel–Crafts alkylation with carbocation intermediates using a microreactor.
24. For acid-catalyzed dehydration of alcohols via carbocation intermediates in a microflow system.
25. For Ritter reaction in a microflow system.
26. Hoffmann-Emery, F.; Hilpert, H.; Scalone, M.; Waldmeier, P. J. Org. Chem. 2006, 71, 2000–2008. doi:10.1021/jo0523666
27. Sorensen, B.; Rohde, J.; Wang, J.; Fung, S.; Monzon, K.; Chiu, W.; Pan, L.; Deng, X.; Stolarik, D.; Frevert, E. U.; Jacobson, P.; Link, J. T. Bioorg. Med. Chem. Lett. 2006, 16, 5958–5962. doi:10.1016/j.bmcl.2006.08.129
28. Becker, C. L.; Engstrom, K. M.; Kerdsky, F. A.; Tolle, J. C.; Wiagaw, S. H.; Wang, W. Org. Process Res. Dev. 2008, 12, 1114–1118. doi:10.1021/op080065q
29. Wang, Z.; Laine, D. I.; Yan, H.; Zhu, C.; Widdowson, K. L.; Buckley, P. T.; Burman, M.; Foley, J. J.; Sarau, H. M.; Schmidt, D. B.; Webb, E. F.; Belmonte, K. E.; Palovich, M. Bioorg. Med. Chem. Lett. 2009, 19, 4560–4562. doi:10.1016/j.bmcl.2009.07.006
30. Barton, V.; Ward, S. A.; Chadwick, J.; Hill, A.; O’Neill, P. M. J. Med. Chem. 2010, 53, 4555–4559. doi:10.1021/jm1002001
31. Shmailov, A.; Alimbarova, L.; Shokova, E.; Tafeenko, V.; Vatsourov, I.; Kovailev, V. Tetrahedron 2010, 66, 3058–3064. doi:10.1016/j.tet.2010.02.043
32. Mukherjee, A.; Wu, Q.; Le Noble, W. J. J. Org. Chem. 1994, 59, 3270–3274. doi:10.1021/jo00091a010
33. Alford, J. R.; Cuddy, B. D.; Grant, D.; McKervey, M. A. J. Chem. Soc., Perkin Trans. 1 1972, 2707–2713. doi:10.1039/P19720002707
License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the Beilstein Journal of Organic Chemistry terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.7.149