SPECIAL ISSUE PAPER

Flow Friedel-Crafts alkylation of 1-adamantanol with arenes using HO-SAS as an immobilized acid catalyst

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INTRODUCTION 1

Organic synthesis routinely uses Brønsted acids, such as hydrochloric acid, sulfuric acid, and *p*-toluene sulfonic acid, as catalyst. However, some of acid catalysts are corrosive and require neutralization prior to being disposed of as wastes. In this regard, the use of heterogeneous solid acid catalysts has distinct advantages over that of homogeneous acid catalysts in terms of safe handling, no need for neutralization after the reaction, and easy separation from products allowing for reuses of the catalyst.^[1] In recent years, flow reaction technology has been adopted in a wide range of organic synthesis.^[2] The combination of a heterogeneous solid acid catalyst and continuous flow system has several important features: (a) a reaction space capable of keeping catalysts in large excess to substrates, (b) a rapid heat exchange through the wall

of a flow reactor, and (c) no need for separation of products from the catalyst.^[3,4]

During the course of our study on flow organic synthesis,^[5] we came across the silica-gel based heterogeneous acid catalyst, hydroxy-substituted sulfonic acidfunctionalized silica (HO-SAS),^[6] sulfonic acid-modified silica gel bearing β -hydroxy functionality. This catalyst is particularly useful in terms of thermal stability (up to 130°C) and enhanced acidity due to the β -hydroxy substitution. Indeed, in our previous works using a flow-setup based on a packed bed reactor containing HO-SAS (Figure 1), we were able to conduct flow Fischer esterification reaction (Scheme 1, Equation 1)^[7] and flow dehydration reaction of allylic alcohols (Scheme 1, Equation $2^{[8,9]}$ with a short period of residence time. Friedel-Crafts alkylation reaction starting with alcohols is a highly green process,^[10,11] since water is the only byproduct as in the cases of Fischer esterification and dehydration of alcohols. In this communication, we

Abstract

Flow Friedel-Crafts alkylation was studied using hydroxy-substituted sulfonic acid-functionalized silica as a catalyst and 1-adamantanol as a model substrate. The reaction of 1-adamantanol (1a) with toluene (2a) proceeded well with 5 min of residence time at 120°C to give good yield of 1-tolyladamantane (3a) as a 1:9 mixture of meta and para isomers. When the flow synthesis was carried out over 2.5 hr of running time, the collected five fractions contain the product **3a** in 97–92% yields, suggesting the durability of the catalyst.

KEYWORDS

1-aryladamantanes, flow Friedel-Crafts alkylation, hydroxy-substituted sulfonic acidfunctionalized silica

Dedicated to the memory of Prof. Jun-ichi Yoshida.

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report the HO-SAS-catalyzed Friedel–Crafts alkylation reaction of 1-adamantanol in flow (Scheme 1, Equation 3). Previous work on Friedel–Crafts alkylation reaction of 1-adamantanol employed an equimolar amount of triflic acid and ionic liquid, such as BMIM



FIGURE 1 Flow set-up for acid catalysis using HO-SAS and a stain-less-steel packed-bed reactor



SCHEME 1 Concept: flow acid catalysis using HO-SAS as an immobilized catalyst

TABLE 1

(OTf),^[12] which required biphasic workup. Consequently, we were pleased to find that the flow Friedel–Crafts alkylation reaction of 1-adamantanol by HO-SAS catalyst proceeded smoothly to give good yields of 1-aryladamantanes.

First, as a model study, the HO-SAS-catalyzed Friedel-Crafts alkylation of 1-adamantanol (1a) and toluene (2a) was investigated using both batch and flow reactors (Table 1). Using a glass-made reactor, the reaction of 1a (0.08 M) and 2a HO-SAS (377 mg, 100°C, 2 hr) proceeded to give 1-p-tolyladamantane (3a) in a yield of 70% with a ratio of o/m/p = 0/10/90 (Entry 1). Then we examined the reaction using a flow setup shown in Figure 1: a stainless-steel column (4.0 mm id \times 50 mm length) filled with HO-SAS (377 mg, 0.155 mmol as -SO₃H moiety), for which a back pressure regulator was connected to the end of the column reactor. Thus, a toluene solution of 1-adamantanol ([1a] = 0.08 M) was introduced to the above catalyst-packed column, which was immersed in an oil bath heated to 100°C. At this temperature, product 3a was obtained in a yield of 59% with a residence time of 30 min (Entry 2). When the oil bath temperature was raised to 120°C, 3a was obtained with a yield of 83% with the same ratio of o/m/p = 0/10/90(Entry 3). Then the flow reaction was carried out with a shorter residence time and, to our delight, it was found that the product yield could be maintained even with a residence time of 5 min (Entry 4).^[13] On the other hand, further shortening the reaction time caused a decrease of the yield (Entry 5, Entry 6). The high efficiency of the present flow catalysis owes to a large catalyst/substrate ratio of 3.7 as well as immediate washing out of water from the catalyst area.

Using the same flow-setup and optimized conditions (Entry 4 in Table 1),^[14] we then studied the reaction of 1-adamantanol (**1a**) and toluene (**2a**) over a prolonged



Batch and flow Friedel-Crafts alkylation of 2a and 1a using HO-SAS

Yield (%)^{a,b} Entry **Reaction mode** Temp. (°C) **Reaction time** 1 Batch 100 2 hr 70 2 Flow 100 30 min 59 Flow 3 120 30 min 83 Flow 82 4 120 5 min 5 Flow 120 2 min 58 52 6 Flow 120 1 min

^aToluene solution of **1a** (0.08 M) was used. Isolated yields by silica gel chromatography are given. ^b**3a** contains 10% of *meta* isomer.



SCHEME 2 Time course for the flow reaction of **2a** and **1a** using HO-SAS



SCHEME 3 Flow Friedel–Crafts alkylation using HO-SAS

operation time (2.5 hr) (Scheme 2). After discarding the first flow fraction that had eluted over the first 10 min, each fraction was collected every 30 min. It was revealed that the product **3a** was obtained in a similarly high yield of 97–92% in each of these fractions, suggesting the durability of the acid catalyst.

We also examined the reaction of **1a** with some other aromatic compounds using the optimized conditions (120°C, 5 min) and the results are summarized in Scheme 3. The Friedel-Crafts alkylation reaction of 1-adamantanol (1a) with anisole (2b) proceeded well to give 1-(methoxyphenyl) adamantane (3b) in 75% yield (o/m/p = 32/0/68). Similarly the reaction of 1-adamantanol (1a) with o-xylene (2c) gave the corresponding 1-(3,4-xylyl)adamantane (3c) in 93% yield. On the other hand, benzene (2d) exhibited a modest reactivity, resulting in the formation of 1-phenyladamantane (3d) in 30% yield. The reaction of *t*-BuOH with toluene (2a) gave arylation product 3e in a low yield with the ratio of o/m/p = 0/10/90. The modest efficiency may be attributed to the competing dehydration of t-BuOH leading to isobutene. These reactions proceeded with para-preference. The absence of ortho isomers for the cases of 3a and 3e is ascribed to steric effects between tertiary alkyl cations and methyl groups. On the other hand, the observation of a significant amount of *ortho* isomer for **3b**, is due to a strong electron-donating effect of a methoxy group, which has been well precedented in Friedel–Crafts alkylation reactions.^[15]

In summary, using HO-SAS as an immobilized acid catalyst in a packed-bed reactor, we have shown that flow Friedel-Crafts alkylation reaction of 1-adamantanol (1a) with typical arenes proceeded well at 120°C to give good yields of the corresponding 1-aryladamantanes. Extremely shortened reaction (residence) time in flow is compared favorably to that of a batch reaction (5 min vs. 2 hr). These results could be rationalized by a high catalyst/substrate ratio available for flow packed bed reactor system. The time course experiment for the flow synthesis of 3a over the period of 2.5 hr proved the durability of the catalytic activity, which is presumably based on the fact that water is washed out consistently from the packed bed reactor. The protocol is operationally simple, thus bypassing tedious workup procedures required for a batch process. We are now extending the utility of flow acid catalysis based on HO-SAS to some other cationic reaction processes.

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REFERENCES

- [1] For selected reviews on heterogeneous acid catalysts, see: a)T. Okuhara, Chem. Rev. 2002, 102, 3641. b) J. A. Melero, J. Iglesias, G. Morales, Green Chem. 2009, 11, 1285. c) M. E. Borges, L. Diaz, Renew. Sust. Energ. Rev. 2012, 16, 2839. d) F. Su, Y. H. Guo, Green Chem. 2014, 16, 2934. e) F. Liu, K. Huang, A. Zheng, F.-S. Xiao, S. Dai, ACS Catal. 2018, 8, 372. f) K. Nakajima, M. Hara, ACS Catal. 2012, 2, 1296 For reviews on heterogeneous acid catalysts using Amberlyst, see: R. Pal, T. Sarkar, S. Khasnobis, Arkivoc, 2012, 570. For reviews on heterogeneous acid catalysts using Nafion, see: g)G. A. Olah, P. S. Iyer, G. K. S. Prakash, Synthesis 1986, 7, 513. h) K. Mazaahir, C. Ritika, B. Shilpi, Curr. Org. Chem 2015, 19, 72. For reviews on heterogeneous acid catalysts using sulfonic acid functionalized silica (SAS), see: i)P. Gholamzadeh, G. M. Ziarani, N. Lashgari, A. Badiei, P. Asadiatouei, J. Mol. Catal. A: Chem. 2014, 391, 208. j) G. M. Ziarani, N. Lashgari, A. Badiei, J. Mol. Catal. A: Chem. 2015, 397, 166.
- For selected reviews on flow chemistry, see: a)T. Fukuyama,
 T. Totoki, I. Ryu, *Green Chem* 2014, 16, 2042. b B. Gutmann,
 D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed* 2015, 54, 6688.

c) H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noel, *Chem. Soc. Rev.* 2016, *45*, 83. d) R. Karande, A. Schmid, K. Buehler, *Org. Process Res. Dev.* 2016, *20*, 361. e) S. Kobayashi, *Chem. Asian J.* 2016, *11*, 425. f) D. L. Hughes, *Org. Process Res. Dev.* 2018, *22*, 13. g) A. R. Bogdan, A. W. Dombrowski, *J. Med. Chem.* 2019, *62*, 6422. h) M. Marcus, T. S. Moody, M. Smyth, S. Wharry, *Org. Process Res. Dev.* 2020, *24*, 1802. i) M. Power, E. Alcock, G. P. McGlacken, *Org. Process Res. Dev.* 2020, *24*, 1814.

- [3] For examples on flow acid catalysis, see: polymer-supported sulfonic acid:a)R. Amandi, P. Licence, S. K. Ross, O. Aaltonen, M. Poliakoff, Org. Process Res. Dev. 2005, 9, 451. b) A. A. Kulkarni, K.-P. Zever, T. Jacobs, A. Kienlea, Ind. Eng. Chem. Res. 2007, 46, 5271. c) M. Rueping, T. Bootwicha, H. Baars, E. Sugiono, J. Beilstein, Org. Chem. 2011, 7, 1680. d) S. Nishimura, A. Shibata, K. Ebitani, ACS Omega 2018, 3, 5988. e) J. S. Kwon, H. Choo, J. -W. Choi, J. Jae, D. J. Suh, K.-Y. Lee, J.-M. Ha, Appl. Catal. A: Gen. 2019, 570, 238. f) H. Hu, H. Ota, H. Baek, K. Shinohara, T. Mase, Y. Uozumi, Y. M. A. Yamada, Org. Lett 2020, 22, 160. polymer-supported phosphoric acidg) A. K. Mutyala, N. T. Patil, Org. Chem. Front. 2014, 1, 582. h) L. Osorio-Planes, C. Rodriguez-Escrich, M. Pericas, A. Miquel, Chem. Eur. J 2014, 20, 2367. polymer supported boronic acidi) Y. Du, T. Barber, S. E. Lim, H. S. Rzepa, I. R. Baxendale, A. Whiting, Chem. Commun. 2019, 55, 2916.
- [4] For recent work on flow catalysis using silica supported sulfonic acid (SAS), see: M. H. Tucker, A. J. Crisci, B. N. Wigington, N. Phadke, R. Alamillo, J. Zhang, S. L. Scott, J. A. Dumesic, ACS Catal 2012, 2, 1865.
- [5] For our recent work on flow chemistry, see: a)M. Ueda, N. Imai, S. Yoshida, H. Yasuda, T. Fukuyama, I. Ryu, Eur. J. Org. Chem 2017, 2017, 6483. b) S. Sumino, M. Uno, T. Fukuyama, I. Ryu, M. Matsuura, A. Yamamoto, Y. Kishikawa, J. Org, Chem 2017, 82, 5469. c) S. Inuki, K. Sato, T. Fukuyama, I. Ryu, Y. Fujimoto, J. Org. Chem. 2017, 82, 1248. d) T. Fukuyama, Y. Fujita, H. Miyoshi, I. Ryu, S.-C. Kao, Y.-K. Wu, Chem. Commun 2018, 54, 5582. e) S. Masui, Y. Manabe, K. Hirao, A. Shimoyama, T. Fukuyama, I. Ryu, K. Fukase, Synlett 2019, 30, 397. f) S.-C. Kao, Y.-C. Lin, I. Ryu, Y.-K. Wu, Adv. Synth. Catal. 2019, 361, 3639. g) H. Watanabe, M. Takemto, K. Adachi, Y. Okuda, A. Dakegata, T. Fukuyama, I. Ryu, K. Wakamatsu, A. Orita, Chem. Lett 2020, 49, 409. Also see reviews: h)T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, Synlett 2008, 151. i) T. Fukuyama, I. Ryu, Radical chemistry by using flow microreactor technology. in Encyclopedia of Radicals in Chemistry, Biology, and Materials, Vol. 2 (Eds: A. Studer, C. Chatgilialoglu), Wiley, Chichester 2012, p. 1243. j) S. Sumino, T. Fukuyama, I. Ryu, Radical chemistry in flow. in Science of Synthesis: Free Radicals: Fundamentals and Applications in Organic Synthesis (Eds: L. Fensterbank, C. Ollivier), Georg Thieme Verlag, Stuttgart, in press.
- [6] Supplied from MiChS Co. Ltd.K. Nobuhara, N. Inoue, M. Kamimura, Jpn. Kokai Tokkyo Koho, JP 2010-203 2010, 794, 16.http://www.michs.jp and Fuji Silysia Chemical Ltd. The amount of sulfonic acid group immobilized on HO-SAS is estimated as 0.41 mmol per gram of HO-SAS
- [7] A. Furuta, T. Fukuyama, I. Ryu, Bull. Chem. Soc. Jpn. 2017, 90, 607.
- [8] A. Furuta, Y. Hirobe, T. Fukuyama, I. Ryu, Y. Manabe, K. Fukase, *Eur. J. Org. Chem.* 2017, 2017, 1365.

- [9] a) H. Fujii, T. Yamada, K. Hayashida, M. Kuwada, A. Hamasaki, K. Nobuhara, S. Ozeki, H. Nagase, *Heterocycles* 2012, 85, 2685. b) S. Masui, Y. Manabe, K. Hirao, A. Shimoyama, T. Fukuyama, I. Ryu, K. Fukase, *Synlett* 2019, 30, 397. c) Y. -L. Tseng, M. -C. Liang, I. -C. Chen, Y. -K. Wu, *Synlett* 2018, 29, 609.
- [10] For recent work on Friedel-Crafts alkylation reactions using benzyl and allyl alcohols, see: a)B. Michelet, U. Castelli, E. Appert, M. Boucher, K. Vitse, J. Marrot, J. Guillard, A. Martin-Mingot, S. Thibaudeau, Org. Lett. 2020, 22, 4944. b) R.-J. Tang, T. Milcent, B. Crousse, J. Org. Chem. 2018, 83, 14001. c) L. Bering, K. Jeyakumar, A. P. Antonchick, Org. Lett. 2018, 20, 3911. d) D. Vukovic, E. Richmond, E. Wolf, J. Moran, Angew. Chem. Int. Ed. 2017, 56, 3085. e) A. Suarez, M. Gohain, M. A. Fernandez-Rodriguez, R. Sanz, J. Org. Chem. 2015, 80, 10421. f) X. Mo, J. Yakiwchuk, J. Dansereau, J. A. McCubbin, D. G. Hall, J. Am. Chem. Soc. 2015, 137, 9694. g) M. Bandini, M. Tragni, Org. Biomol. Chem. 2009, 7, 1501. Also see a review: e)M. Rueping, B. J. Nachtsheim, Beilstein J. Org. Chem 2010, 6 (6). https://doi.org/10.3762/bjoc.6.6.
- [11] For flow Friedel-Crafts acylation, see: a)S. Suga, A. Nagaki, J. i. Yoshida, *Chem. Commun.* 2003, 354. b) A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. T. McQuade, *Angew. Chem. Int. Ed.* 2009, 48, 8547. c) D. R. Snead, T. F. Jamison, *Angew. Chem. Int. Ed.* 2015, 54, 983. d) H. Koo, H. Y. Kim, K. Oh, *Org. Lett.* 2019, 21, 10063. e) H. Koo, Y. Kim, K. Oh, *Org. Chem. Front.* 2019, 6, 1868.
- [12] Triflic acid is used for arylation of 1-adamantanol, see: a)K. K. Laali, V. D. Sarca, T. Okazaki, A. Brock, P. Der, Org. Biomol. Chem. 2005, 3, 1034. b) A. Wrona-Piotrowicz, A. Makal, J. Zakrzewski, J. Org. Chem. 2020, 85, 11134.
- [13] Typical procedure: 1-adamantanol (1a, 65 mg, 0.43 mmol) was dissolved in toluene (2a, 5.0 ml, 47.2 mmol) and placed in a syringe equipped with a syringe pump. This solution was fed into a stainless steel-made column (4.0 mm × 50 mm) filled with HO-SAS (A, 377 mg, 0.155 mmol as -SO₃H moiety), the flow rate was 0.097 ml/min. This column was immersed in an oil bath (120°C). The reaction mixture firstly eluted for 10 min was discarded, and the latter eluted reaction mixture was collected for 10 min, evaporated to give the crude product which was purified with column chromatography on SiO₂ to give the product 3a (16 mg, 0.068 mmol, 82% yield). ¹H NMR (500 MHz, CDCl₃): 1.79 (m, 6H), 1.94 (m, 6H), 2.12 (m, 3H), 2.35 (s, 3H), 7.18 (d, 2H, J = 7.8 Hz), 7.30 (d, 2H, J = 7.8 Hz). These chemical shifts were consistent with the literatureC. Lohre, T. Droge, C. Wang, F. Glorius, Chem. Eur. J. 2011, 17, 6052.
- [14] Time course experiment: 1-adamantanol (1a) (383 mg, 2.51 mmol) was dissolved in toluene (30 ml), and transferred (flow rate = 0.096 ml/min) by a HPLC pump. The methanol solution was fed into a stainless steel column (4.0 mm \times 50 mm) filled with HO-SAS (A, 362 mg). A back-pressure regulator (40 psi) was connected to the end of the tube. Then, the column was immersed into an oil bath (120°C). The reaction mixture firstly eluted for 10 min was discarded. The following portions were collected every 30 min (total fifth time) in glass flasks and analyzed by GC. The combined reaction mixture was evaporated and the crude product was purified

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with column chromatography on SiO_2 to give the product **2a** (254 mg, 92%, 1.12 mmol).

[15] G. A. Olah, J. A. Olah, T. Ohyama, J. Am. Chem. Soc. 1984, 106, 5284.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article. **How to cite this article:** Kasakado T, Hyodo M, Furuta A, Kamardine A, Ryu I, Fukuyama T. Flow Friedel–Crafts alkylation of 1-adamantanol with arenes using HO-SAS as an immobilized acid catalyst. *J Chin Chem Soc.* 2020;1–5. <u>https://doi.</u> org/10.1002/jccs.202000518