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Pictet–Spengler reactions catalyzed by Brønsted acid-surfactant-combined catalyst in water or aqueous media

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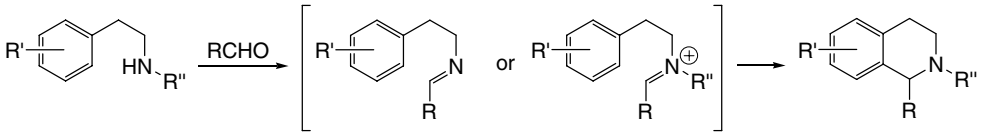
Abstract—Perfluorooctanesulfonic acid (PFOSA), Brønsted acid-surfactant-combined catalyst, efficiently catalyzes the Pictet–Spengler reactions of β-arylethyl carbamate derivatives with aldehydes in water. The present reaction is accelerated by the addition of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP).

Recently, water and aqueous reaction media attract much interest not only for the viewpoint of green chemistry, but also for unique physical and chemical properties of water.[1] A variety of efficient catalytic systems in water has been developed and, in particular, Lewis acid- or Brønsted acid-surfactant-combined catalyst (LASC[2] or BASC[3,4]) is notable for playing a concomitant role in activation and solubilization of organic substrates. For example, *n*-dodecylbenzenesulfonic acid (DBSA) as BASC was found to work well for dehydration reactions such as the esterification and etherification in water as well as three-component Mannich-type reactions including dehydrative formation of imine derivatives.[3] It could be explained that the inside of emulsion droplets composed of substrate and DBSA is hydrophobic enough to exclude water molecules. Thus, surfactant catalyzed organic reactions in water have become one of the most challenging research topics.

The Pictet–Spengler reaction provides us with a convenient method for synthesis of tetrahydroisoquinoline and β-carboline derivatives,[5,6] which are found in many natural and synthetic alkaloids possessing important biological activities.[7] The Pictet–Spengler reaction involves the cyclization of imines or iminium ions formed by the dehydration reaction of β-arylethylamine derivatives with aldehydes (Scheme 1). In nonaqueous solvent, the catalytic reactions have been achieved by the use of Lewis acid,[8] Brønsted acid,[9] organocatalyst[10] or zeolite-type reagent.[11] Although the reactions in water or aqueous media have been known, they require large excess of strong Brønsted acid or have the limitation in reactants.[12] In this letter, we report the perfluorooctanesulfonic acid (PFOSA)-catalyzed Pictet–Spengler reaction in water.

About the Pictet–Spengler reactions of β-arylethylamine in water, it has been reported that the hydrochloride salt of 3,4-dimethoxyphenethylamine (**1**) gave no cyclized product.[12a,13] The reaction of 3,4-dimethoxy-phenethylamine carbamate **2**, which was expected to form a reactive *N*-acyl iminium intermediate,[14,15] ended with the



Scheme 1.

Keywords: Surfactant; Brønsted acid; Pictet–Spengler reaction; Carbamate; Isoquinoline.
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recovery of **2** in water even in the presence of hydrochloric or sulfuric acid (1 equiv). Screening of miscellaneous Brønsted acid catalysts for the reaction of carbamate **2** with *n*-heptanal in water at rt (Table 1), the use of 20 mol % *n*-dodecyl-benzenesulfonic acid (DBSA), which is known as BASC,[3] gave the desirable cyclized product **3a** in 27% yield, while **2** was recovered in 69% (entry 1). Although Brønsted acids such as trifluoroacetic acid (TFA), *p*-toluenesulfonic acid (TsOH) and trifluoromethanesulfonic acid (TfOH) have been reported to be good catalysts for the Pictet–Spengler reactions in organic solvents,[15,16] they were not effective catalysts in water (entries 2–4). *n*-Perfluorooctanesulfonic acid (PFOSA),[17,18] however, significantly accelerated the cyclization of **2** giving rise to **3a** in 90% yield (entry 6).

Since an addition of alcohol to aqueous surfactant has been known to show changes in the properties of surfactant,[19] we investigated the additive effect of alcohol (3 equiv to substrate) in the reaction of **2** with *n*-heptanal (1.2 equiv) in the presence of PFOSA (20 mol%) at rt for 4 h (Fig. 1). Compared with hydrocarbon alcohols, the fluorinated alcohol, in particular, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) exerted a marked effect on the formation of **3a**. In the presence of HFIP as an additive, **2** was consumed at rt within 4 h to give **3a** in 99% yield, in which the concentration of HFIP in water corresponds to 11.5 v/v% (Table 1, entry 10). HFIP showed its efficiency for the use of DBSA as well (entry 11), while the reaction with TfOH was only slightly accelerated (entry 12). The sole use of HFIP did not yield **3a** in the absence of the catalyst (entry 13). Although it is expected that the additive effect of HFIP takes part in the enhancement of acidity of catalyst,

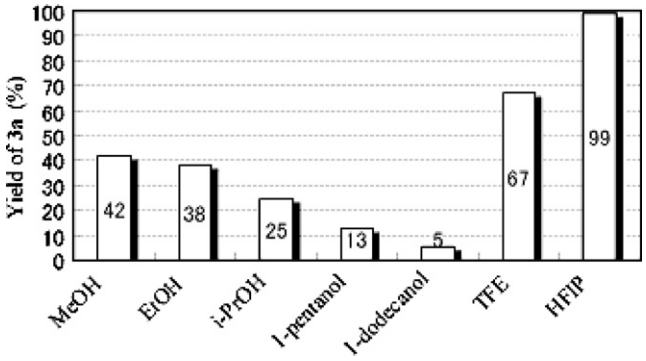
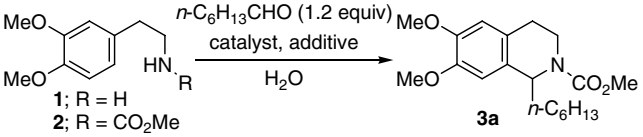


Figure 1. Additive effect of alcohol (3 equiv to **2**) in the PFOSA (20 mol %)-catalyzed reaction of **2** with *n*-heptanal (1.2 equiv) at rt for 4 h in water (1 mL). (Yield of **3a** was determined by ^{1}H NMR. TFE; 2,2,2-tirfluoroethanol, HFIP; 1,1,1,3,3,3-hexafluoro-2-propanol).

there has been a marked difference in pH for each catalyst (PFOSA, DBSA or TfOH) solution in HFIP–water.[20] The addition of *i*-PrOH was inferior to that of HFIP even in the reaction with hydrocarbon surfactant (entry 9).[21] It should be mentioned that HFIP-water concentration profile in Figure 2 leads to 10–20 v/v% as the optimum concentration for PFOSA-catalyzed reaction of **2** with *n*-heptanal.[22] The use of less amount of PFOSA (5 or 10 mol %) as a catalyst required a prolonged reaction time and higher temperature to afford product **3a** in an excellent yield (entries 14 and 15).

As shown in Table 2, regardless of the presence of HFIP, water-soluble aldehydes (R = Et, H, *i*-Pr) showed

Table 1. Screening of Brønsted acid catalysts in water[a]



Entry	Catalyst[b] (mol %)	Additive[b] (equiv)	Temperature, time (h)	Yield[c] (%)	
				3a	**2**
1	DBSA (20)	—	rt, 18	27	69
2	TFA (20)	—	rt, 18	—	99
3	TsOH (20)	—	rt, 18	2	97
4	TfOH (20)	—	rt, 18	4	92
5	TfOH (20)	SDS (0.2)	rt, 18	11	89
6	PFOSA (20)	—	rt, 18	90 (84)	—
7	NaPFOSA (30)	—	rt, 18	3	95
8	PFOSA (20)	*i*-PrOH (3)	rt, 4	25	75
9	DBSA (20)	*i*-PrOH (3)	rt, 4	14	85
10	PFOSA (20)	HFIP (3)	rt, 4	99 (97)	—
11	DBSA (20)	HFIP (3)	rt, 4	99 (95)	—
12	TfOH (20)	HFIP (3)	rt, 4	21	75
13	—	HFIP (3)	rt, 4	—	99
14	PFOSA (10)	HFIP (3)	rt, 24	99 (97)	—
15	PFOSA (5)	HFIP (3)	60, 24	99 (99)	—

[a] Reaction concentration: **2**/water = 0.42 mmol/1 mL.
[b] Equivalent to **2**.
[c] Yield was determined by ^{1}H NMR with toluene as an internal standard, and yield in parentheses was an isolated yield.

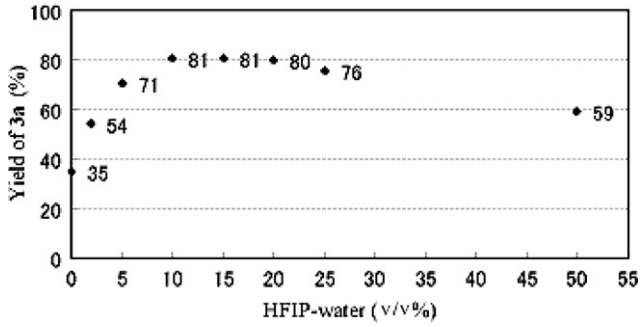


Figure 2. HFIP-water concentration profile for the PFOSA (20 mol %)-catalyzed reaction of **2** with *n*-heptanal (1.2 equiv) at rt for 1.5 h. (Yield of **3a** was determined by ^{1}H NMR.)

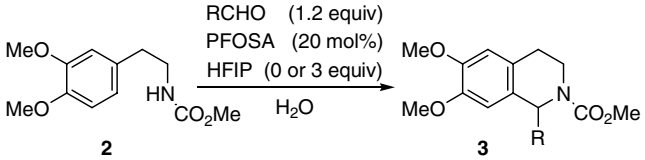
the inferior reactivities to that of water-insoluble aldehydes (R = *n*-hexyl, *n*-dodecyl, Cy). A similar observation has been reported in the DBSA catalyzed esterification of carboxylic acids with alcohols in water.[3b] It has been suggested that hydrophobic carboxylic acid and/or alcohol readily assemble together with DBSA through hydrophobic interactions to form emulsion droplets and the hydrophobicity of substrates as well as DBSA facilitate the dehydration in water.[3b] In the present reaction, hydrophobic substrates and PFOSA in the absence of HFIP would be considered to form an analogous hydrophobic area enough to exclude water molecules. Although the role of HFIP is unclear,[23] the hydrophobic fluorinated alcohol might have a beneficial effect for the aggregation of substrates and PFOSA in water.

The effect of substituent on the aromatic ring was examined (Table 3). When *m*-tyramine derivative **4** was employed, the reactions with both *n*-heptanal and benzaldehyde proceeded smoothly, and the corresponding para-cyclized products **5a** and **5e** were obtained as a major isomer, respectively (entries 3 and 4). Likewise, 3-MeO substituted derivative **6** afforded good results (entries 5 and 6). On the other hand, carbamate **8**, which has no activating substituent, was not engaged in the cyclization reaction (entries 7 and 8).

To gain a better understanding whether intermolecular Friedel–Crafts type reaction of aryl core of substrate with aldehyde prior to the formation of the *N*-acyl iminium intermediate takes part in the present reaction, we attempted the reaction of 3,4-dimethoxybenzene **9** with *n*-heptanal (Scheme 2). Under the similar condition to **2** (Table 1, entry 6), the presumed product **10** was not obtained even at 90 °C for 40 h. By taking into consideration of *N*-acyl iminium ion-activated Pictet–Spengler or Mannich reaction,[14,15] the present process involves *N*-acyl iminium intermediate as shown in Scheme 1 rather than the intermolecular Friedel–Crafts type reaction.

In conclusion, we demonstrated that efficient PFOSA catalyzed Pictet–Spengler reactions of β-arylethyl carbamate derivatives with various aldehydes in water. The addition of HFIP was found to accelerate the catalytic reaction remarkably. Further studies on the scope of substrates and the detail effect of HFIP are underway.

Table 2. Pictet–Spengler reactions of **1** with various aldehydes[a]

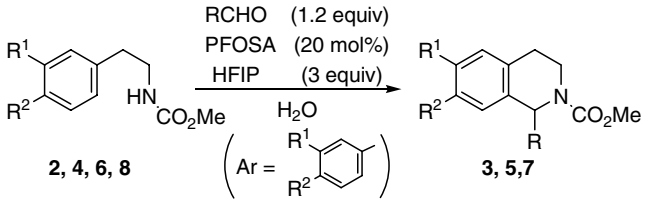


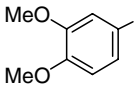
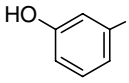
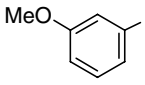
2 **3**

Entry	R–CHO	HFIP (equiv)	Condition		3[b] (%)	
			(°C)	(h)		
1	$CH_3(CH_2)_5CHO$	3	rt	4	**3a**	97
2	$CH_3(CH_2)_5CHO$	—	rt	18	**3a**	84
3	$CH_3(CH_2)_{10}CHO$	3	rt	4	**3b**	90
4	$CH_3(CH_2)_{10}CHO$	—	60	18	**3b**	92
5	EtCHO	3	rt	10	**3c**	95
6	EtCHO[c]	—	60	5	**3c**	99
7	Formaline (37%)	3	rt	8	**3d**	86
8	Formaline (37%)	—	60	2	**3d**	93
9	PhCHO	3	90	19	**3e**	94
10[d]	PhCHO	—	90	18	**3e**	81
11	*i*-PrCHO[e]	3	90	20	**3f**	96
12	CyCHO[e]	3	90	4	**3g**	99
13	*t*-BuCHO	3	90	18	**3h**	—

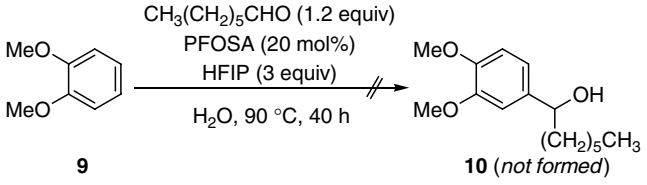
[a] Reaction concentration: **2**/water = 0.42 mmol/1 mL.
[b] Isolated yield.
[c] 2.5 equiv.
[d] PFOSA:1.2 equiv.
[e] 1.8 equiv.

Table 3. Pictet–Spengler reactions of various carbamates[a]



Entry	Ar	R–CHO	Condition (°C)	Condition (h)	Product[b] (%)	
1	 **2**	$CH_3(CH_2)_5CHO$	rt	4	**3a**	97
2		PhCHO	90	19	**3e**	94
3	 **4**	$CH_3(CH_2)_5CHO$	rt	4	**5a**	90 (7.6:1)[c]
4		PhCHO	90	18	**5e**	84 (16:1)[c]
5	 **6**	$CH_3(CH_2)_5CHO$	rt	10	**7a**	95 (14:1)[c]
6		PhCHO	90	5	**7e**	99 (16:1)[c]
7	 **8**	$CH_3(CH_2)_5CHO$	90	8	—	
8		PhCHO	90	2	—	

[a] Reaction concentration: substrate/water = 0.42 mmol/1 mL.
[b] Isolated yield.
[c] Regioisomer ratio (*para*/*ortho* cyclized product).



Scheme 2.

Acknowledgements

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References and notes

1. (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blakie Academic and Professional: London, 1998; (b) Li, C.-J.; Chan, t.-H. *Organic Reactions in Aqueous Media*; John Wiley and Sons: New York, 1997.
2. (a) Kobayashi, S.; Wakabayashi, T. *Tetrahedron Lett.* **1998**, *39*, 5839; (b) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 7202; (c) Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F. *Chem. Commun.* **2005**, 789; (d) Wang, L.; Han, J.; Tian, H.; Sheng, J.; Fan, Z.; Tang, X. *Synlett* **2005**, 337.
3. (a) Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* **1999**, 1401; (b) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971; (c) Aoyama, N.; Kobayashi, S. *Chem. Lett.* **2006**, *35*, 238.
4. (a) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426; (b) Akiyama, T.; Takaya, J.; Kagoshima, H. *Adv. Synth. Catal.* **2002**, *334*, 338.
5. Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.
6. For reviews: (a) Bringmann, G.; Ewers, C. L. J.; Walter, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, Vol. 6, Chapter 4.2; (b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.
7. For reviews: (a) Brown, R. T. In *Indoles*; Saxton, J. E., Ed.; Wiley Interscience: New York, 1983, Part 4 (The Monoterpenoid Indole Alkaloids); (b) Bentley, K. W. *Nat. Prod. Rep.* **2004**, *21*, 395, and references cited therein.

8. Manabe, K.; Nobutou, D.; Kobayashi, S. *Bioorg. Med. Chem.* **2005**, *13*, 5154.
9. Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086.
10. Taylar, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.
11. Hegedus, A.; Hell, Z. *Tetrahedron Lett.* **2004**, *45*, 8553.
12. (a) Kovacs, O.; Fodor, G. *Chem. Ber.* **1951**, *84*, 795; (b) Freter, K.; Huebner, H.; Metz, H.; Schroeder, H. D.; Zeile, K. *Just. Liebigs Ann. Chem.* **1965**, *684*, 159; (c) Kawai, M.; Deng, Y.; Kimura, I.; Yamamura, H.; Araki, S.; Naoi, M. *Tetrahedron: Asymmetry* **1997**, *9*, 1487; (d) Kametani, T.; Fukumoto, K.; Katagi, T. *Chem. Pharm. Bull.* **1959**, *7*, 567.
13. In our preliminary research, the reactions of 3,4-dimethoxyphenethylamine hydrochloride with *n*-heptanal afforded no cyclized product in water.
14. For review: Maryanoff, B. E.; Zhang, C.-H.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.
15. Recent example: Danetz, J. R.; Ciccolini, R. P.; Froling, M.; Paap, S. M.; Allen, A. J.; Holmes, A. B.; Tester, J. W.; Danheiser, R. L. *Chem. Commun.* **2005**, 4465.
16. (a) Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327; (b) Yokoyama, A.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1999**, *64*, 611.
17. Critical micelle concentration: 6.9 mM (by electric conductivity analysis).
18. Perfluoroalkylsulfonic acid-catalyzed reactions in aqueous media: Nishikido, J. JP Patent 2001-328954, 2001.
19. Zana, R. *Adv. Colloid Interface Sci.* **1995**, *57*, 1.
20. We have carried out the pH determination of catalyst (80 μmol) solutions in HFIP (130 μL)–water (1 mL) by pH meter. PFOSA:1.15. DBSA:1.21. TfOH:1.15.
21. It has been reported that fluorinated alcohols are more strongly partitioned in the micelles with both the hydrocarbon and fluorocarbon surfactants than hydrocarbon alcohols. See: Muto, J.; Yoda, K.; Yoshida, N.; Esumi, K.; Meguro, K.; Binana-Limbele, W.; Zana, R. *J. Colloid Interface Sci.* **1989**, *130*, 165, See also Ref. 19.
22. In dry HFIP, **2** was consumed at rt within 1.5 h and isoquinoline **3a** was obtained in 92% yield. However, the use of 3 equiv HFIP in water (the concentration of HFIP corresponds to 11.5 v/v%) is appropriate not only for the viewpoint of green chemistry, but also for the efficiency of the reaction of **2** in water.
23. Clustering of HFIP in water has been reported: (a) Hong, D.-P.; Hoshino, M.; Kuboi, R.; Goto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 8427; (b) Yoshida, K.; Yamaguchi, T.; Adachi, T.; Otomo, T.; Matsuo, D.; Takamuku, T.; Nishi, N. *J. Chem. Phys.* **2003**, *119*, 6132.