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Hydrophobic Polymer-Supported Catalyst for Organic Reactions in Water: Acid-Catalyzed Hydrolysis of Thioesters and Transprotection of Thiols

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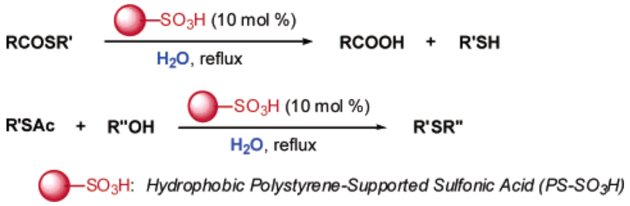
ABSTRACT



A hydrophobic polystyrene-supported sulfonic acid was found to be effective for hydrolysis of thioesters in pure water. It was revealed that the catalyst was much superior to other Brønsted acid catalysts. Transprotection of thiols from thioesters to thioethers has been successfully performed in water using this catalytic system.

Organic reactions in water without the use of any harmful organic solvents are of great current interest, because water is an easily available, economical, safe, and environmentally benign solvent.[1] Although various catalysts have been developed to realize organic transformation in water,[2] it is still difficult to achieve recovery and reuse of the catalysts in many cases. On the other hand, organic reactions using polymer-supported catalysts have received much attention because of easy workup and reuse of the catalysts.[3] For polymer-supported catalysts that work efficiently in water, hydrophobic interactions between the polymers and organic substrates would play an important role in catalytic activity.[4] This idea encouraged us to use a hydrophobic polymer-supported catalyst in water. In this paper, we disclose that a hydrophobic polystyrene-supported sulfonic acid not only is a recoverable and reusable catalyst but also is much more active than other Brønsted acids in the hydrolysis of thioesters.[5]

Thioesters are synthetically useful as well as biologically important compounds, partly because they are versatile

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(1) (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997.

(2) Reviews: (a) *Aqueous-Phase Organometallic Catalysis. Concepts and Applications*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim; 1998. (b) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209.

(3) (a) Kobayashi, S. *Curr. Opin. Chem. Biol.* **2000**, *4*, 338. (b) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Laech, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815.

(4) For recent examples of polymer-supported catalysts that work in water, see: (a) Nagayama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 567. (b) Bergbreiter, D. E.; Liu, Y.-S. *Tetrahedron Lett.* **1997**, *38*, 7843. (c) Bergbreiter, D. E.; Case, B. L.; Liu, Y.-S.; Caraway, J. W. *Macromolecules* **1998**, *31*, 6053. (d) Chen, C.-W.; Chen, M.-Q.; Serizawa, T.; Akashi, M. *Chem. Commun.* **1998**, 831. (e) Danjo, H.; Tanaka, D.; Hayashi, T.; Uozumi, Y. *Tetrahedron* **1999**, *55*, 14341. (f) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919. (g) Sakamoto, T.; Pac, C. J. *Tetrahedron Lett.* **2000**, *41*, 10009. (h) Yamada, Y. M. A.; Ichinohe, M.; Takahashi, H.; Ikegami, S. *Org. Lett.* **2001**, *3*, 1837. (i) Masaki, Y.; Yamada, T.; Tanaka, N. *Synlett* **2001**, 1311.

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protecting groups for thiols or carboxylic acids.[6] In general, hydrolysis of thioesters to thiols and carboxylic acids is carried out under basic conditions. However, problems with this method are that oxidation of thiols to disulfides is prone to occur and that more than equimolar amounts of the reagents are needed. Although acid-promoted hydrolysis of thioesters provides an alternative important method, it is not common because of high activation energies for the acid-promoted hydrolysis,[7,8] requiring the use of excess amounts of strong acids such as 6 N HCl.[9] Furthermore, acid-catalyzed hydrolysis of water-insoluble thioesters in water without using organic cosolvents is extremely difficult to realize. Therefore, we undertook development of an acid catalyst for hydrolysis of water-insoluble thioesters.

We examined the catalytic activity of various Brønsted acids in a model reaction of hydrolysis of dodecyl thiolaurate (Table 1). As expected, the hydrolysis did not proceed at all without a catalyst (entry 1) or with several Brønsted acids (entries 2−6) under water-reflux conditions for 24 h, even when carried out in 3 N H_2SO_4 (the amount of the catalyst is 900 mol %) or 6 N HCl (the amount of the catalyst is 3600 mol %) (entries 5 and 6). In addition, a surfactant-type Brønsted acid such as *p*-dodecylbenzenesulfonic acid (DBSA), which is effective for several organic reactions in water,[10] was also inactive (entry 7). On the other hand, it was exciting to find that a hydrophobic polystyrene-supported sulfonic acid (PS-SO_3H, 0.462 mmol/g) prepared by sulfonation of 1% DVB cross-linked polystyrene (200−400 mesh) was effective for the hydrolysis (entry 8). However, a commercially available DOWEX 50W-X2 (a sulfonated, cross-linked polystyrene, H form, 4.41 mmol/g) was ineffective (entry 9). Whereas PS-SO_3H scarcely swelled in water, DOWEX 50W-X2 swelled well in water because of the difference in sulfonic acid content.[11] This result indicates that the highly hydrophobic nature of polymer-supported catalysts plays a very important role for catalytic activity.[5e] Another type of polymer-supported sulfonic acid, Nafion-H,[12] was found to be inactive (entry 10).

Table 1. Hydrolysis of Thioester with Various Brønsted Acid Catalysts

$$C_{11}H_{23}COSC_{12}H_{25} \xrightarrow[H_2O,\ reflux,\ 24\ h]{catalyst\ (10\ mol\ \%)} C_{11}H_{23}COOH + C_{12}H_{25}SH$$

entry	catalyst	yield (%)[a]
1	None	0
2	TsOH	0
3	TfOH	0
4	$C_8F_{17}SO_3H$	0
5	H_2SO_4[b]	0
6	HCl[c]	0
7	DBSA	2
8	PS-SO_3H[d]	69
9	DOWEX 50W-X2[d]	0
10	Nafion-H[d]	0

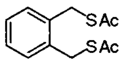
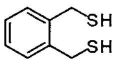
[a] NMR yield. [b] In 3 N H_2SO_4 (900 mol %). [c] In 6 N HCl (3600 mol %). [d] 10 mol % of SO_3H group.

Interestingly, mixed solvents such as H_2O/1,4-dioxane (1/1) and H_2O/toluene (1/1), giving 21% and 33% yields under reflux conditions for 24 h, respectively, were not good for the PS-SO_3H-catalyzed hydrolysis of the thioester, indicating that pure water is the most effective solvent system in this hydrolysis. This result is one of the characteristic features of this system.

Next, we investigated substrate generality in the PS-SO_3H-catalyzed hydrolysis of thioesters in water (Table 2). The reactions proceeded smoothly to give the corresponding thiols or carboxylic acids in high to excellent yields for various types of thioesters. Although the reaction time was longer, only 2 mol % of PS-SO_3H was enough to catalyze the hydrolysis (entry 7). It is also noteworthy that formation of disulfides, which often occurs under basic conditions, was not at all observed even when the hydrolysis of the substrate

Table 2. PS-SO_3H-Catalyzed Hydrolysis of Various Substrates

$$RCOSR' \xrightarrow[H_2O,\ reflux,\ 24\ h]{PS\text{-}SO_3H\ (10\ mol\ \%)} RCOOH + R'SH$$

entry	substrate	product	yield (%)[a]
1	$C_{11}H_{23}COSC_{12}H_{25}$	$C_{11}H_{23}COOH$ $C_{12}H_{25}SH$	95[b] 95[b,c]
2	$C_{11}H_{23}COSEt$	$C_{11}H_{23}COOH$	93[d]
3	$C_{11}H_{23}COS^tBu$	$C_{11}H_{23}COOH$	quant.[e]
4	$C_{11}H_{23}COSPh$	$C_{11}H_{23}COOH$	98
5	$Ph(CH_2)_2COSEt$	$Ph(CH_2)_2COOH$	85
6	(*E*)-PhCH=CHCOSEt	(*E*)-PhCH=CHCOOH	90[e]
7	$AcSC_{12}H_{25}$	$C_{12}H_{25}SH$	quant.[f] (quant.)[g]
8	$AcSCH_2Ph$	$PhCH_2SH$	80
9	$AcS(CH_2)_3Ph$	$Ph(CH_2)_3SH$	quant.
10	$PhCOSC_{12}H_{25}$	$C_{12}H_{25}SH$	89[e,h,i]
11			99

[a] Isolated yield. [b] 72 h. [c] Containing disulfide (2%). [d] 36 h. [e] 168 h. [f] Under air. [g] PS-SO_3H (2 mol %), 48 h. [h] PS-SO_3H (20 mol %). [i] Containing disulfide (5%).

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(5) Polymer-supported sulfonic acid catalyzed hydrolysis of oxoesters has been reported; see: (a) Thomas, G. G.; Davies, C. W. *Nature* **1947**, *159*, 372. (b) Haskell, V. C.; Hammett, L. P. *J. Am. Chem. Soc.* **1949**, *71*, 1284. (c) Sakurada, I.; Sakaguchi, Y.; Ono, T.; Ueda, T. *Makromol. Chem.* **1966**, *91*, 243. (d) Yoshikawa, S.; Kim, O.-K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1515. Quite recently, we reported use of polymer-supported sulfonic acids for oxoester formation in water: (e) Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2002**, *344*, 270.

(6) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.

(7) Bruice, T. C. In *Organic Sulphur Compounds*; Kharasch, N., Ed; Pergamon Press: London, 1961; Vol. 1, p 421 and references therein.

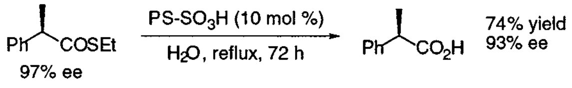
(8) Recently, we have developed the first example of Brønsted acid catalyzed intermolecular direct thioesterification of carboxylic acids with thiols: Iimura, S.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2002**, 94.

(9) For examples of acid-promoted hydrolysis of thioesters, see: (a) Garbiras, B. J.; Marburg, S. *Synthesis* **1999**, 270. (b) Bergeron, R. J.; Wiegand, J.; Weimar, W. R.; Vinson, J. R. T.; Bussenius, J.; Yao, G.-W.; McManis, J. S. *J. Med. Chem.* **1999**, *42*, 95. (c) Effenberger, F.; Isak, H. *Chem. Ber.* **1989**, *122*, 553.

shown in entry 7 was carried out under air atmosphere. In addition, PS-SO_3H was recoverable and reusable (eq 1). These results demonstrate that this hydrolysis of thioesters provides a general and useful method to deprotect thiols or carboxylic acids.

$$C_{12}H_{25}SAc \xrightarrow[\text{H}_2\text{O, reflux, 24 h}]{\text{PS-SO}_3\text{H (10 mol \%)}} C_{12}H_{25}SH \qquad \begin{matrix}\text{1st: quant.}\\ \text{2nd: quant.}\\ \text{3rd: quant.}\end{matrix} \qquad (1)$$

It is a significant problem that racemization is often observed when hydrolysis of thioesters is carried out under basic conditions. However, PS-SO_3H-catalyzed hydrolysis of an optically active thioester, ethyl (*R*)-(−)-2-phenylthiopropionate, proceeded with only slight loss of enantiomeric excess under water-reflux conditions (eq 2).[13] Therefore, this is one of the advantages of the acid-catalyzed hydrolysis of thioesters.



(2)

By carrying out the hydrolysis of thioesters in the presence of benzylic alcohols, transprotection of thiols was realized in water. The reactions proceeded smoothly to give benzylic thioethers from thioesters in good yields (Table 3).[14] It is interesting to note that, under the reaction conditions, opposite types of reactions (hydrolysis and dehydration)[10e,f] occur in the same pot. This system provides an effective method for conversion of thioesters to benzylic thioethers without isolating the intermediates, thiols.

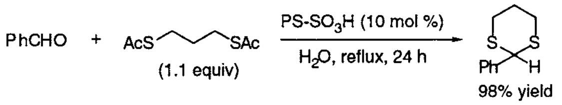
In addition, an almost odorless dithioester instead of a dithiol, which has an unpleasant odor, can be used directly for dithioacetalization of a carbonyl compound (eq 3).[10e,f,15] To the best of our knowledge, this is the first example of dithioacetalization using dithioesters.

Table 3. PS-SO_3H-Catalyzed Transprotection of Thiols in Water

$$\text{RSAc} + \text{R'OH} \xrightarrow[\text{H}_2\text{O, reflux, 48 h}]{\text{PS-SO}_3\text{H (10 mol \%)}} \text{RSR'}$$

entry	RSAc	R'OH (equiv)	yield (%)[a]
1	$C_{12}H_{25}SAc$	Ph_3COH (1.0)	91 (86)[b]
2	$C_{12}H_{25}SAc$	Ph_2CHOH (2.0)	90
3	$C_{12}H_{25}SAc$	4-$MeOC_6H_4CH_2OH$ (2.0)	71
4	$PhCH_2SAc$	Ph_3COH (1.0)	88[b]

[a] Isolated yield. [b] 24 h.



(3)

In summary, we have found that a hydrophobic polystyrene-supported sulfonic acid is effective for hydrolysis of thioesters in pure water and that the catalyst is much superior to other Brønsted acid catalysts, including a surfactant-type Brønsted acid. Transprotection of thiols from thioesters to benzylic thioethers has also been realized in water using this catalytic system. This work will provide a new aspect of catalytic organic reactions in water as well as an atom-economical,[16] simple, and practical method for hydrolysis of thioesters.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* **1999**, 1401. (b) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965. (c) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537. (d) Manabe, K.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10101. (e) Kobayashi, S.; Iimura, S.; Manabe, K. *Chem. Lett.* **2002**, 10. (f) Manabe, K.; Iimura S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971.

(11) PS-SO_3H (0.755 mmol/g) gave 10% yield under the conditions shown in Table 1.

(12) The sulfonic acid content was estimated as 0.930 mmol/g from acid−base titration.

(13) Significant racemization was observed in the hydrolysis of ethyl (*R*)-(−)-2-phenyl-thiopropionate (97% ee) under basic conditions: NaOMe/MeOH (rt, 2 h), NaOH/H_2O/1,4-dioxane (rt, 10 h), LiOH/H_2O/THF (rt, 30 h), and $Ba(OH)_2$/H_2O/THF (rt, 72 h) gave 95% yield (Me ester, 46% ee), 97% yield (33% ee), 89% yield (27% ee), and 81% yield (36% ee), respectively.

(14) The thioetherification of dodecanethiol and benzyl alcohol with PS-SO_3H hardly proceeded in water.

(15) For a recent example of organic reactions using odorless thiols, see: Node, M.; Kumar, K.; Nishide, K.; Ohsugi, S.; Miyamoto, T. *Tetrahedron Lett.* **2001**, *42*, 9207.

(16) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233.