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The effects of aromatic and aliphatic anionic surfactants on $Sc(OTf)_3$-catalyzed Mukaiyama aldol reaction in water

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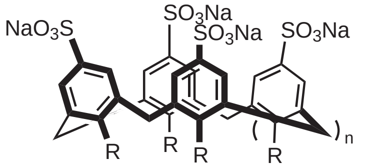
Abstract—Aromatic (**2c** and **2d**) and aliphatic (**2a** and **2b**) anionic surfactants were employed in $Sc(OTf)_3$-catalyzed aldol reactions of some labile silyl enol ethers (**3a** and **3b**) with aromatic aldehydes in water. The results indicated that the aromatic surfactants have a better ability to inhibit the hydrolysis of labile silyl enol ethers and promote the aldol reaction, leading to higher yields of aldol adducts. © 2001 Elsevier Science Ltd. All rights reserved.

Organic reactions in water, which avoid the use of harmful organic solvents, are now of great interest especially in relation to today's environmental concerns.[1] Recently, great progress has been made on the lanthanide triflate catalysed Mukaiyama aldol reaction in aqueous media,[2] and even in pure water. However, some surfactants must be added[3] to promote the reactions in water alone. These surfactants can be anionic, such as sodium dodecyl sulfate (SDS), or non-ionic. In addition, although some very labile silyl enol ethers can react smoothly with aldehydes in water in the presence of a Lewis acid-surfactant-combined catalyst, such as scandium trisdodecylsulfate (STDS),[4] they decompose rapidly in a $Sc(OTf)_3$–SDS–H_2O system, leading to a low yield of the desired products. In order to improve the reaction yield, it is necessary to use a large excess of the labile silyl enol ethers. More recently, we reported[5] that the calix[6]arene derivatives **1** bearing sulfonate groups on the upper rim and the alkyl groups on the lower rim have a special ability as surfactants in stabilizing labile silyl enol ethers and in promoting the aqueous Mukaiyama reaction. In view of the molecular structure, it should be noted that the calix[6]arene derivative can be considered as a bundle of aromatic anionic surfactants, while SDS is an aliphatic anionic surfactant. Therefore, considering the different effects of aromatic and aliphatic surfactants, it would be interesting to investigate the roles of aromatic and aliphatic anionic surfactants in the $Sc(OTf)_3$-catalyzed Mukaiyama aldol reaction in water.



1 n=3
R=n-C_4H_9, or n-C_6H_{13}

In our investigations, aliphatic anionic surfactants sodium dodecyl sulfate (**2a**) and sodium dodecylsulfonate (**2b**), and aromatic anionic surfactants sodium *p*-dodecylphenylsulfate (**2c**) and sodium *p*-dodecylphenylsulfonate (**2d**), were used.[6] Among them, **2c** is not commercially available and can be prepared by Fridel–Crafts reaction, followed by Zn–Hg reduction and reaction with sulphur trioxide/pyridine.[7] Since aqueous solutions of **2c** are likely to decompose at ambient temperature within several days, freshly prepared **2c** must be used in the aqueous reaction. Initial reactions of 1-trimethylsiloxy-cyclohex-1-ene (**3a**) with aldehydes **4a–d** were carried out in water at room temperature in the presence of the surfactants **2a–d** (20 mol%) and the catalyst $Sc(OTf)_3$ (10 mol%) to afford the aldol products **5a–d** (Eq. (1)). The experimental results are summarized in Table 1. In the case of alkyl sulfonate surfactant **2a**, the silyl enol ether **3a** in the reaction mixtures disappeared (as shown by TLC) after 1–1.5 h; however, a large amount of the aldehydes remained, leading to lower yields of aldol products (40–54%, entry 1, 5, 9). On the other hand, in the presence of the corresponding aryl sulfonate surfactant **2c**, the yields of the aldol products were very high (88–99%, entry 3, 7, 11, 14) with the same reaction time. For sodium alkyl and aryl sulfonates (**2b** and **2d**), the same trend was observed: sodium alkyl sulfate **2b**

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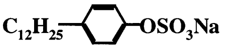
furnished lower yields (55–70%, entry 2, 6, 10) and sodium aryl sulfate **2d** higher yields (78–93%, entry 4, 8, 12) of the aldol products, respectively. For *p*-chlorobenzaldehyde **4d**, both sodium alkyl and aryl sulfates (**2a** and **2c**) gave higher yields (entry 13 and 14) due to a higher reactivity of **4d**. Meanwhile, a significant difference between **2a** and **2c** (74 and 98% yields, respectively) was observed. Both aromatic and aliphatic surfactants offer a similar stereoselectivity (*syn*/*anti*) of the aldol reaction products.

$C_{12}H_{25}OSO_3Na$

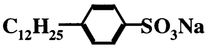
2a

$C_{12}H_{25}SO_3Na$

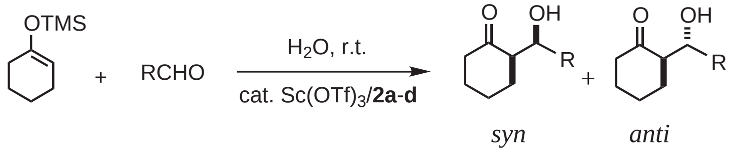
2b



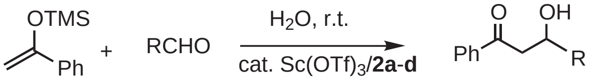
2c



2d



3a **4a-d** **5a-d** (1)



3b **4a-b** **5e-f** (2)

The reactions of 1-trimethylsiloxy-1-phenyl-ethylene **3b** with aldehydes **4a**–**b** were also carried out in water in the presence of the surfactants **2b** and **2d** (Eq. (2)). Again a trend was noticed in which the yields of the aldol products **5e** and **5f** were lower (43–49%; entry 15, 17) for the aliphatic anionic surfactant than those for the aromatic anionic surfactant under the same reaction conditions. It should be noted that no reaction was observed between **3b** and aldehydes either in the absence of surfactants or with sulfonated calix[6]arene itself as the surfactant.[5]

It was assumed that micelles were formed in these reaction systems and that the Lewis acid-catalyzed reactions would proceed smoothly in these micelles. On the other hand, there is a competition between the hydrolysis of the silicon substrate and the $Sc(OTf)_3$-catalyzed aldol reaction of silyl enol ether with aldehydes in aqueous media. The hydrolysis of the silicon substrates has a strong effect on the yield of the corresponding aqueous aldol reaction. In the case of **2a** and **2b**, the silyl enol ethers (**3a** and **3b**) in the reaction mixture disappeared (as shown by TLC) after 1 h of the reaction, leading to lower yields of the aldol products. Therefore, although hydrolysis of some labile silyl enol ether can be prevented by using alkyl sulfates and sulfonates to some extent, the hydrolysis reaction still surpasses the desired aldol reaction in aqueous media. From these results we can conclude that the surfactants with aryl groups can inhibit the hydrolysis of labile silyl enol ethers (**3a** and **3b**) and promote the aldol reactions more effectively than the alkyl surfactants. These results suggest that the micellar phases with **2a**–**d**

Table 1. Aqueous aldol reactions of silyl enol ethers with aldehydes in the presence of various surfactants

Entry	Aldehyde (R)	Silyl enol ether	Surfactant	Reaction time (h)	Product (R)	Yield[a] (%) (*syn*/*anti*)
1	Ph, **4a**	**3a**	**2a**	1	Ph, **5a**	47 (72/28)
2	**4a**	**3a**	**2b**	1	**5a**	55 (68/32)
3	**4a**	**3a**	**2c**	1	**5a**	99 (80/20)
4	**4a**	**3a**	**2d**	1	**5a**	85 (75/25)
5	*p*-CH_3OPh, **4b**	**3a**	**2a**	1.5	*p*-CH_3OPh, **5b**	40 (61/39)
6	**4b**	**3a**	**2b**	1.5	**5b**	61 (63/37)
7	**4b**	**3a**	**2c**	1.5	**5b**	98 (69/31)
8	**4b**	**3a**	**2d**	1.5	**5b**	93 (73/27)
9	PhCH=CH, **4c**	**3a**	**2a**	1	PhCH=CH, **5c**	54 (52/48)
10	**4c**	**3a**	**2b**	1	**5c**	70 (49/51)
11	**4c**	**3a**	**2c**	1	**5c**	88 (50/50)
12	**4c**	**3a**	**2d**	1	**5c**	78 (51/49)
13	*p*-ClPh, **4d**	**3a**	**2a**	1	*p*-ClPh, **5d**	74 (77/23)
14	**4d**	**3a**	**2c**	1	**5d**	98 (77/23)
15	**4a**	**3b**	**2b**	1	Ph, **5e**	49
16	**4a**	**3b**	**2d**	1	**5e**	61
17	**4b**	**3b**	**2b**	1	*p*-CH_3O, **5f**	43
18	**4b**	**3b**	**2d**	1	**5f**	58

[a] Yields based on ^1H NMR.

provide an excellent reaction medium for organic reactions by passivating the lability of **3a** and **3b** by sequestration within their hydrophobic cavities. It should also be noted that the yield of the reaction of **3a** with a simple aliphatic aldehyde, such as nonyl aldehyde, in the presence of aromatic surfactant **2d** was very low (10%). The silyl enol ether **3a** disappeared within 0.5 h, generating a complicated mixture of products. The π–π interaction between the molecules of aryl surfactant and aryl aldehydes would be more favourable for activation of the substrates in the hydrophobic cavities. An alternative interpretation of the low yield between **3a** and nonyl aldehyde is that two micelle populations exist, one of which is stabilized by nonyl aldehyde and the other which is stabilized by **2d**, thereby effectively keeping the two reactants in separate microenvironments. In summary, aromatic surfactants provide better protection of labile silyl enol ethers and promote the aldol reaction more effectively than aliphatic surfactants.[8]

Acknowledgements

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6. The critical micelle concentrations of **2a**, **2b**, and **2d** are 0.0081, 0.0098, and 0.0016 mol/L, respectively, see: *The Application of Surfactants in Pharmaceutics*; Zhong, J. F., Ed.; The People's Press of Hygiene: Beijing, 1996, p. 114. The critical micelle concentration of **2c** is not known and should be comparable to the others. Based on the concentrations of surfactants being used, all reactions should proceed above the critical micelle concentrations.
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8. A typical experimental procedure is as follows: A mixture of benzaldehyde (0.2 mmol), silyl enol ether **3** (0.3 mmol), surfactant **2** (0.2 equiv.), and $Sc(OTf)_3$ (10 mg, 0.1 equiv.) in water (1 mL) was stirred at room temperature until the silyl enol ether disappeared on TLC. The mixture was then passed through a short silica gel pad and extracted with ethyl ether. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired aldol adduct.