Facile synthesis of α-amino phosphonates in water using a Lewis acid–surfactant-combined catalyst

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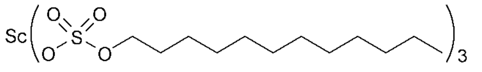
Received (in Cambridge, UK) 7th January 2000, Accepted 6th March 2000
Published on the Web 30th March 2000

Three-component reactions of aldehydes, amines and triethyl phosphite were efficiently catalyzed by scandium tris(dodecyl sulfate) at ambient temperature in water to give various *α*-amino phosphonates in high yields.

α-Amino phosphonates constitute an important class of biologically active compounds, and their synthesis has been a focus of considerable attention in synthetic organic chemistry as well as in medicinal chemistry.[1] Most synthetic methods reported utilize reactions of imines with phosphorus nucleophiles. Recently, it has been shown that three-component reactions of aldehydes (or ketones), amines, and diethyl phosphite [HOP(OEt)$_2$] were efficiently promoted by catalytic amounts of Lewis acids such as ytterbium triflate[2] and indium chloride[3] in dichloromethane (CH_2Cl_2) or THF at ambient temperature. Although these procedures do not require the isolation of the unstable imines prior to the reactions, reaction times of longer than 10 h are necessary to obtain the desired products in good yields at room temperature. In addition, the use of harmful organic solvents such as CH_2Cl_2 is undesirable from the viewpoint of today's environmental consciousness.

In the course of our investigations to develop environmentally friendly synthetic methods, we have found that surfactant-type Lewis acids function as effective catalysts for aldol reactions in water without using organic solvents.[4] The catalysts, which we denote Lewis acid–surfactant-combined catalysts (LASCs), consist of Lewis acidic metal cations such as scandium(III) and amphiphilic anions such as dodecyl sulfate, and form stable colloidal dispersions in the presence of organic substrates in water. Here we report that scandium tris(dodecyl sulfate) **1**, a representative LASC, effectively catalyzes three-component reactions of aldehydes, amines and triethyl phosphite [P(OEt)$_3$] in water to give α-amino phosphonates in high yields.



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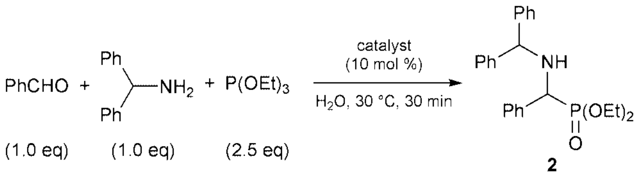
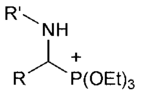
First, the reaction of benzaldehyde, benzhydrylamine and P(OEt)$_3$ was tested as a model reaction in the presence of various catalysts in water (Table 1). When LASC **1** was used as a catalyst, the reaction proceeded smoothly to afford the desired product **2** in good yield (entry 1). On the other hand, sodium dodecyl sulfate (SDS) or scandium triflate gave **2** in very low yields (entries 2 and 3). These results indicate that both the Lewis acidic cation and the anionic surfactant are indispensable for the efficient catalysis. LASC **1** was much superior to dodecylbenzenesulfonic acid (DBSA, entry 4), a surfactant-type Brønsted acid which has been successfully used for three-component Mannich-type reactions in water.[5] Furthermore, the reaction under neat conditions without any solvents proceeded slowly (entry 5), indicating that water as a solvent plays an essential role for acceleration of the reaction. It was interesting to find that a reaction with HOP(OEt)$_2$, which has been used as a phosphorus nucleophile in the Lewis acid-catalyzed synthesis of α-amino phosphonates in organic solvents,[2,3] scarcely proceeded (entry 6). Thus, the use of P(OEt)$_3$ instead of HOP(OEt)$_2$ is a characteristic of our system. Mechanistically, P(OEt)$_3$ attacks an imine, which is formed from an aldehyde and an amine *in situ* and then activated by the Lewis acid, to generate phosphonium intermediate **3**. In contrast to the reactions in organic solvents, hydrolysis of **3** to the corresponding phosphonate should occur rapidly in water without causing any side reactions. This rapid hydrolysis makes the use of P(OEt)$_3$ possible in the present catalytic system. Unfortunately, an excess of P(OEt)$_3$ is needed at the present stage, since it is gradually hydrolyzed to HOP(OEt)$_2$ in water. Under the same reaction conditions as those in entry 1, the reaction in the absence of the amine afforded only a trace amount of diethyl 1-hydroxy-1-phenylmethylphosphonate. This result indicates that imines are activated by **1** more effectively than aldehydes.

Table 1 Three-component synthesis of α-amino phosphonate **2** in water



Entry	Catalyst	Yield(%)
1	**1**	71
2	SDS (30 mol %)	8
3	Sc(OTf)$_3$	6
4	DBSA	18
5[a]	**1**	31
6[b]	**1**	Trace

[a] Under neat conditons. [b] HOP(OEt)$_2$ (2.5 eq.) was used instead of P(OEt)$_3$.



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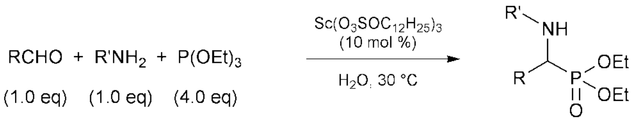
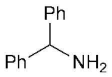
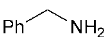
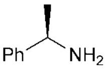
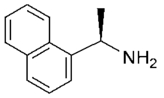
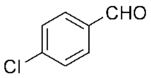
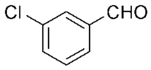
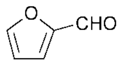
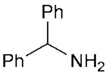
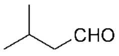
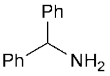
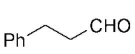
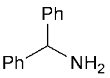
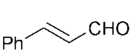
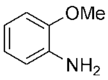
The reactions of various aldehydes and amines with P(OEt)$_3$ in the presence of **1** in water gave the corresponding α-amino phosphonates in high yields as shown in Table 2.† Not only benzaldehyde (entries 1–6) but also other aromatic (entries 7 and 8), heteroaromatic (entry 9) and aliphatic aldehydes (entries 10 and 11) worked well to give the phosphonates in high yields, although α,β-unsaturated aldehydes such as cinnamaldehyde (entry 12) afforded the desired products in lower yields. A characteristic point of these reactions is the extremely short reaction time. When using aniline-type amines such as aniline

DOI: 10.1039/b000319k

Table 2 Three-component synthesis of α-amino phosphonates in water



Entry	RCHO	R'NH$_2$	*t*/min	Yield (%)
1	PhCHO		60	83
2	PhCHO	PhNH$_2$	20	88
3	PhCHO		20	86
4	PhCHO		60	84
5	PhCHO		60	78[a]
6	PhCHO		60	80[b]
7		PhNH$_2$	30	85
8		PhNH$_2$	20	80
9			120	78
10			60	83
11			60	95
12			20	53

[a] 56% de. [b] 61% de.

and *o*-anisidine, the reaction proceeded rapidly, and > 80% yields of the products were attained in 20–30 min (entries 2, 3, 7, and 8). Thus, the turnover frequencies (TOFs) for these reactions are 17–26 h^{-1}, in contrast to the reported procedures in organic solvents, in which the TOFs are < 1 h^{-1}.[2,3] While several organic reactions in water have been developed so far,[6] most of them proceeded slowly in water compared with the corresponding synthetic methods in organic solvents. It is noted that the use of an LASC, a new type of Lewis acid, creates excellent hydrophobic reaction fields to realize the rapid three-component reactions in water. Use of chiral amines, (*R*)-1-phenylethylamine and (*R*)-1-(1-naphthyl)ethylamine, resulted in modest diastereoselectivities (entries 5 and 6).

In conclusion, three-component reactions of aldehydes, amines and triethyl phosphite were effectively catalyzed by LASC **1** to give various α-amino phosphonates in high yields. It should be noted that these high yields were obtained in water, at ambient temperature, and at high reaction rates. This reaction system not only provides a novel method for the synthesis of biologically important α-amino phosphonates but also extends the applicability of LASCs in organic synthesis in water to lead to environmentally friendly chemical processes.

Notes and references

† *General procedure* for the synthesis of α-amino phosphonates: an amine (0.25 mmol), an aldehyde (0.25 mmol) and P(OEt)$_3$ (1.0 mmol) were successively added to a mixture of LASC **1** (0.025 mmol, 10 mol%) in water (1.5 mL) at 30 °C. The mixture was stirred at the same temperature for 20 –120 min, and then 1 M NaOH (5 mL) was added. After stirring at room temperature for 15–30 min, brine (5 mL) was added, the mixture extracted with ethyl acetate (30 mL), dried over Na$_2$SO$_4$, and concentrated. Purification by silica gel chromatography afforded the desired product.

1 F. Heaney, in *Comprehensive Organic Functional Group Transformations*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Elsevier Science, Oxford, 1995, vol. 4, ch. 4, 10; S. C. Fields, *Tetrahedron*, 1999, **55**, 12 237; E. K. Fields, *J. Am. Chem. Soc.*, 1952, **74**, 1528; R. Tyka, *Tetrahedron Lett.*, 1970, 677; G. H. Birum, *J. Org. Chem.*, 1974, **39**, 209; I. J. W. Huber and M. Middlebrooks, *Synthesis*, 1977, 883; D. Redmore, *J. Org. Chem.*, 1978, **43**, 992; K. Afarinkia, J. I. G. Cadogan and C. W. Rees, *Synlett*, 1990, 415; C. Yuan and S. Chen, *Synthesis*, 1992, 1124; S. Laschat and H. Kunz, *Synthesis*, 1992, 90.
2 C. Qian and T. Huang, *J. Org. Chem.*, 1998, **63**, 4125.
3 R. C. Ranu, A. Hajra and U. Jana, *Org. Lett.*, 1999, **1**, 1141.
4 S. Kobayashi and T. Wakabayashi, *Tetrahedron Lett.*, 1998, **39**, 5389; K. Manabe and S. Kobayashi, *Synlett*, 1999, 547; K. Manabe, Y. Mori and S. Kobayashi, *Tetrahedron*, 1999, **55**, 11 203; K. Manabe and S. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 3773.
5 K. Manabe, Y. Mori and S. Kobayashi, *Synlett*, 1999, 1401; K. Manabe and S. Kobayashi, *Org. Lett.*, 1999, **1**, 1965.
6 *Organic Synthesis in Water*, ed. P. A. Grieco, Blacky Academic and Professional, London, 1998.