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The direct synthesis of thioesters using an intermolecular radical reaction of aldehydes with dipentafluorophenyl disulfide in water

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The combination of the water-soluble radical initiator, 2,2′-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA–044), and surfactant, cetyltrimethylammonium bromide (CTAB), was found to be the most suitable condition for the effective direct synthesis of useful active thioesters (pentafluorophenyl thioesters) in water.

Thioesters are useful synthetic intermediates in organic synthesis.[1] For example, they have been employed as mild acyl transfer reagents,[2] building blocks of heterocyclic compounds[3] for aldol reactions[4] and for the synthesis of ketones[5] and amides.[6] The synthesis of thioesters was achieved from thiols (or equivalent thiol substrates) and activated carboxylic acid derivatives, which were prepared from carboxylic acids using activating reagents.[7] Under these circumstances, the direct synthesis of thioesters from aldehydes using thioanions or thiyl radicals would be a useful method.[8] Especially, no one has reported the direct synthesis of thioesters from aldehydes using thiyl radicals except for Takagi's report.[9] The method is the shortest, but has some disadvantages from the viewpoint of reagent efficiency. Namely, a large amount of the aldehyde is required, since the aldehyde must be used not only as the reagent but also as the solvent. Here we wish to report a highly effective intermolecular radical reaction of C–S bond formation in a micellar system using the combination of a water–soluble initiator (Fig. 1)[10] and surfactant[11] in water. Our method produces useful pentafluorophenyl thioesters, whose utility was already clarified by Davis *et al.*,[6] in high yields, and the reaction is carried out under mild conditions in water.[12] Therefore, much attention is being devoted to this reaction from the viewpoint of green chemistry.[13]

First, we examined the possibility of thioesterifications in water with 3-phenylpropionaldehyde (**1a**) and dipentafluorophenyl disulfide (**2a**) using various water-soluble azo-type initiators and a catalytic amount of CTAB as the first chosen surfactant (Table 1). As a result, we could confirm the formation of thioesters in these systems. VA-044 was found to be the most effective initiator among the initiators used in Table 1 (entry 1). A side-reaction occurred when the typical radical initiator AIBN was used (entry 5), while using Et_3B, a known radical initiator that acts at low temperature, the reaction hardly proceeded at all (entry 6). Next, we examined the effect of surfactants on the reaction using VA–044 in water. The cationic surfactants (CTAC, $CTAHSO_4$) gave the thioesters in good yields (entries 8 and 9). However, the anionic surfactant (SDS), the neutral surfactant (Triton X–100) and tetraethylammonium bromide did not give a satisfactory result (entries 10–12). In the absence of the surfactant, the reaction did not proceed at all (entry 7).

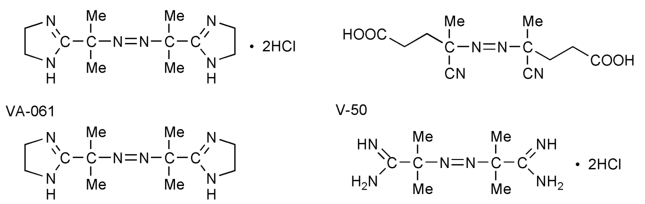


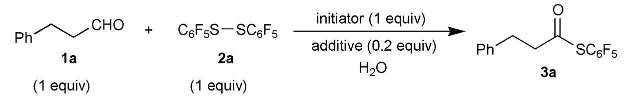
Fig. 1 Water-soluble radical initiators.

The solvent effect on this reaction using **1a**, **2a**, VA–044 and CTAB is shown in Table 2. From these results, water was found to be the best solvent for the thioesterification. The thioesterification did not proceed in benzene or under neat conditions (entries 1–3). In addition, when the radical initiators AIBN, V–70L[14] and Et_3B were used in benzene, the yields of the thioesters were lower than the former cases (entries 4–6).

We then investigated the generality of this pentafluorophenyl thioesterification in water using VA–044 and CTAB, which was the most effective condition. Under these conditions, alkyl and aryl aldehydes (**1b–g**) were smoothly reacted with **2a** to give the corresponding thioesters (**3b–g**) in good yields (Table 3). The yields of the thioesters might be affected by the stabilities of the acyl radical intermediates.[15]

The plausible mechanism of this reaction is shown in Scheme 1.† First, disulfide (**2**) dissociates with the initiator (VA–044) to give the thiyl radical (**A**). Secondly, the hydrogen in the aldehyde (**1**) is trapped by the thiyl radical (**A**), and then the acyl

Table 1 Effect of various initiators and additives



Entry	Initiator	Additive	Temp./°C	Time/h	Yield (%)
1	VA–044	CTAB	50	18	73
2	VA–061	CTAB	80	2	Decomp.
3	V–501	CTAB	70	24	32
4	V–50	CTAB	60	24	45
5	AIBN	CTAB	80	12	37
6	Et_3B	CTAB	rt–50	24	Trace
7	VA–044	None	50	24	No reaction
8	VA–044	CTAC[a]	50	24	67
9	VA–044	$CTAHSO_4$[b]	50	24	63
10	VA–044	SDS[c]	50	24	18
11	VA–044	TritonX–100[d]	50	24	16
12	VA–044	$Et_4N^+Br^-$	50	24	Trace

[a] CTAC: cetyltrimethylammonium chloride. [b] $CTAHSO_4$: cetyltrimethylammonium hydrogen sulfate. [c] SDS: sodium dodecyl sulfate. [d] Triton X-100: polyoxyethylene(10)isooctylphenyl ether.

Table 2 Effect of various solvents and initiators

$$\underset{(1\text{ equiv})}{\mathbf{1a}} + \underset{(1\text{ equiv})}{\mathbf{2a}} \xrightarrow[\text{additive (0.2 equiv)}\\ \text{solvent}]{\text{initiator (1 equiv)}} \mathbf{3a}$$

Entry	Initiator	Solvent	Additive	Temp./°C	Time/h	Yield (%)
1	VA–044	H_2O	CTAB	50	18	73
2	VA–044	Neat	CTAB	50	24	Trace
3	VA–044	Benzene	CTAB	50	24	N.R.[a]
4	AIBN	Benzene	None	80	24	32
5	V–70L	Benzene	None	50	24	29
6	Et_3B	Benzene	None	rt	24	Trace

[a] No reaction.

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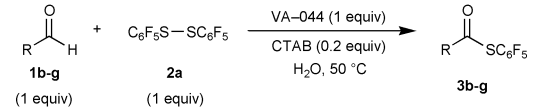
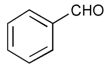
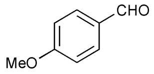
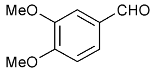
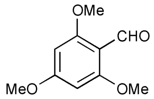
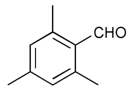
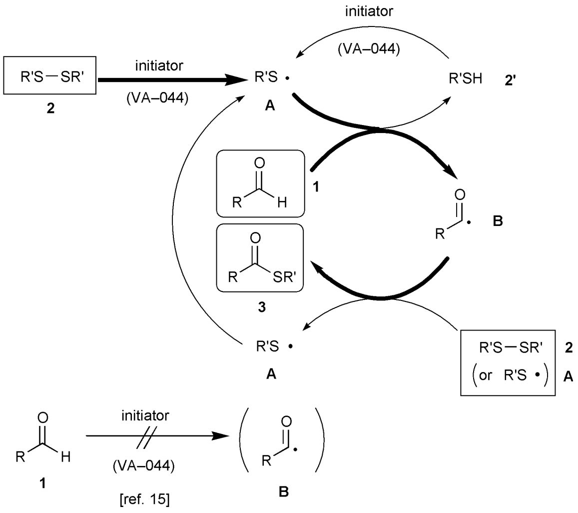
radical (**B**) is formed. The acyl radical reacts with the disulfide (**2**) or thiyl radical (**A**), and the thioesterification (**3**) is achieved. The thiol (**2′**) produced by the reaction of the thiyl radical (**A**) and aldehyde (**1**) becomes the thiyl radical with the initiator, and the thiyl radical (**A**) takes part in the reaction cycle again. Whereas, Chatgilialoglu *et al.* have already reported that alkyl radicals prepared by the initiator did not trap the hydrogen in the aldehyde.[15]

In summary, we have discovered that the combination of a water-soluble radical initiator VA–044 and surfactant CTAB is an ideal reaction system to accomplish C–S bond formation in water. This method is effective for the synthesis of active thioesters under mild conditions, and could be applied using various aldehydes. Moreover, the pentafluorophenyl thioester, which can be prepared by our method, has valuable utilities, since they have already been shown to have a high activity toward various nucleophiles.[6] We believe that our system would become the common method for the thioesterification from the corresponding aldehydes.

Table 3 Application using various aldehydes



Entry	Aldehyde		Time/h	Product	Yield (%)
1	$CH_3(CH_2)_9CHO$	**1b**	8	**3b**	88
2		**1c**	24	**3c**	47
3		**1d**	24	**3d**	56
4		**1e**	24	**3e**	72
5		**1f**	8	**3f**	95
6		**1g**	24	**3g**	90



Scheme 1 A plausible mechanism of thioesterification.

We thank Wako Pure Chemical Industries, Ltd., for the generous supply of several water-soluble azo-type initiators.

Notes and references

† *General procedure*: VA–044 (48.5 mg, 0.15 mmol) was added to a solution of aldehydes (**1a–g**) (0.30 mmol), dipentafluorophenyl disulfide (**2a**) (119 mg, 0.30 mmol) and CTAB (21.9 mg, 0.060 mmol) in H_2O (3 ml) at rt. The reaction mixture was then stirred and heated to 50 °C. After 3 h, an additional amount of the initiator VA–044 (48.5 mg, 0.15 mmol) was added to the reaction mixture. The progress of the reaction was monitored by TLC. The reaction mixture was then extracted with AcOEt, and the organic layer was dried using Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give the pure thioesters **3a–g**.

1 L. Field, *Synthesis*, 1972, 101 and references cited therein.
2 T. Mukaiyama, M. Araki and H. Takei, *J. Am. Chem. Soc.*, 1973, **95**, 4763.
3 C. Alvarez-Ibarra, M. Mendoza, G. Orellana and M. L. Quiroga, *Synthesis*, 1989, 560; R. Annunziata, M. Benaglia, M. Cinquini and F. Cozzi, *Tetrahedron Lett.*, 1995, **36**, 613.
4 T. Mukaiyama, H. Uchiro, I. Shiina and S. Kobayashi, *Chem. Lett.*, 1990, 1019; S. Kobayashi, H. Uchiro, Y. Fujishita, I. Shiina and T. Mukaiyama, *J. Am. Chem. Soc.*, 1991, **113**, 4247.
5 G. J. McGarvey, J. M. Williams, R. N. Hiner, Y. Matsubara and T. Oh, *J. Am. Chem. Soc.*, 1986, **108**, 4943; L. S. Liebeskind and J. Srogl, *J. Am. Chem. Soc.*, 2000, **122**, 11260.
6 A. P. Davis and J. J. Walsh, *Tetrahedron Lett.*, 1994, **35**, 4865; A. P. Davis, S. Menzer, J. J. Walsh and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1996, 453.
7 For example: (i) the coupling of carboxylic acids and thiols using some activating reagents; S. Iimura, K. Manabe and S. Kobayashi, *Chem. Commun.*, 2002, 94 (ii) the coupling of heavy metal thiolates with acid chlorides; G. Spessard, W. K. Chan and S. Masamune, *Org. Synth.*, 1982, **61**, 134 (iii) the coupling of disulfides and carboxylic acids using triphenylphosphine; T. Endo, S. Ikenaga and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 2632.
8 M. Kurauchi, T. Imamoto and M. Yokoyama, *Tetrahedron Lett.*, 1981, **22**, 4985; T. Inoue, T. Takeda, N. Kambe, A. Ogawa, I. Ryu and N. Sonoda, *J. Org. Chem.*, 1994, **59**, 5824.
9 M. Takagi, S. Goto and T. Matsuda, *J. Chem. Soc., Chem. Commun.*, 1976, 92; M. Takagi, S. Goto, M. Tazaki and T. Matsuda, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1982.
10 Y. Kita and M. Matsugi, Radical Initiators. In *Radicals in Organic Synthesis Volume 1* eds. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, p. 1–10; The water-soluble azo type radical initiators used in our studies are available from Wako Pure Chemical Industries, Ltd. Osaka, Japan.
11 *Catalysis in Micellar and Macromolecular Systems*, ed. J. H. Fendler, Academic Press, New York, 1998.
12 *cf.* Radical reaction under micellar condition in water: Y. Kita, H. Nambu, N. G. Ramesh, G. Anilkumar and M. Matsugi, *Org. Lett.*, 2001, **3**, 1157.
13 *Organic Synthesis in Water*, ed. P. A. Grieco, Blackie Academic, London, 1998.
14 Y. Kita, K. Gotanda, C. Ohira, M. Suemura, A. Sano and M. Matsugi, *J. Org. Chem.*, 1999, **64**, 6928 and references cited therein.
15 C. Chatgilialoglu, D. Crich, M. Komatsu and I. Ryu, *Chem. Rev.*, 1999, **99**, 1991 and references cited therein.