Highly efficient synthesis of thioesters in water†

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Thioesters were efficiently prepared *via* the direct reaction of tertiary thioamides and alkyl halides in water, and in the presence of catalytic amounts of NaI, hexadecyltrimethylammonium bromide (HTAB), and 1,4-diazabicyclo[2.2.2]octane (DABCO). Hence, thioamides smoothly undergo an *S*-alkylation with alkyl halides in aqueous media following by hydrolysis to afford the corresponding thioesters in very good to excellent yields.

Introduction

Thioesters represent organic derivatives of wide interest due to their wide range of biological activity and considerable applications in drug development[1–5] and industry.[6–8] Thioesters of coenzyme A (CoA) are ubiquitous in all living organisms and play central roles in their metabolism.[9] In addition, polyketide synthases (PKSs) and nonribosomal polypeptide synthetases (NRPKs) use thioesters of fatty acids and amino acids as key intermediates to assemble bioactive polyketides and peptides.[10-12] Also, thioesters show distinctive chemical properties compared to oxoesters[13] and their enhanced reactivity has successfully been employed in a wide range of synthetic organic transformations.[14] Hence, developing a simple and versatile method for the preparation of thioesters is still an urgent need.

The most well known approach to the synthesis of thioesters is the direct reaction of the corresponding thiols with a suitable acid chloride [15] or acid anhydride.[16-18] Moreover, thioesters have been synthesized by direct reaction of carboxylic acids with thiols and in the presence of diverse reaction conditions and catalysts.[19-21] Thioesters have also been prepared by the reaction of esters[22] or *N*-acylbenzotriazoles[23] with thiols. Recently, *tert*-butyl protected thiols have been utilized for the preparation of thioesters.[24] More recently the *N*–*S* acyl shift, mediated by attaching a thiol auxiliary residue to the peptide backbone, has been applied to peptide thioester syntheses.[25] However, this method employs thiols and long reaction times, and the overall yields are not satisfactory (16–31%). The Dess–Martin periodinane (DMP)-mediated reaction of thiols and aldehydes represents another method for the synthesis of thioesters.[26]

Although most of these approaches provide efficient access to thioesters, they suffer from the use of corrosive reagents, harsh reaction conditions, expensive catalysts or reagents, and unfriendly organic solvents. Nevertheless, the greatest disadvantage of the previously mentioned methods is the application of thiols as starting materials, which are very unpleasant and noxious compounds. However, despite the efficiency of the latter protocols, the development of less expensive and environmentally benign reaction courses is a major goal for organic synthesis. Therefore, we were eager to develop a single-step and quite eco-friendly method for the synthesis of diverse thioesters.

Undoubtedly, thioamides are very important building blocks in organic synthesis and especially in construction of heterocyclic compounds.[27] Herein, we report the first development, to our knowledge, of a straightforward and versatile method to obtain thioesters using tertiary thioamides in aqueous media and in the presence of catalytic amounts of NaI, DABCO, and hexadecyltrimethylammonium bromide (HTAB).

Results and discussion

We started our study with examining the reaction of morpholino (phenyl) methanethione **1a** as a test thioamide starting material, prepared by the Willgerodt–Kindler method,[28] with 4-nitrobenzyl bromide **2a** and in various reaction conditions to produce the corresponding *S*-4-nitrobenzyl benzothioate **3a**.

At the outset of our study, DMF was used as the solvent for the reaction course. Therefore, the starting morpholino (phenyl) methanethione and equimolar amounts of 4-nitrobenzyl bromide were dissolved in small quantities of DMF and the reaction mixture was heated at 95 °C for 40 min. Thereafter, the reaction mixture was treated in the same temperature with catalytic amounts of DABCO in small quantities of water for 20 min to obtain the corresponding thioester in moderate yield (68%). In addition to DMF, other solvents were also examined as reaction media and the screening results indicate a notable increase of the yields in polar solvents (Table 1). These outcomes are in accordance with the ionic nature of the thioformamidinium intermediate salt and the low solubility of such an intermediate in less polar solvents. It is also worthwhile to note that increasing the reaction times and temperatures does not lead to an increase in the yield of thioester, and our investigations revealed that in these conditions the reaction mixture is contaminated with some colored or tarry materials.

According to these results, we were intrigued to investigate the reaction in water as a green solvent. Interestingly, it was found

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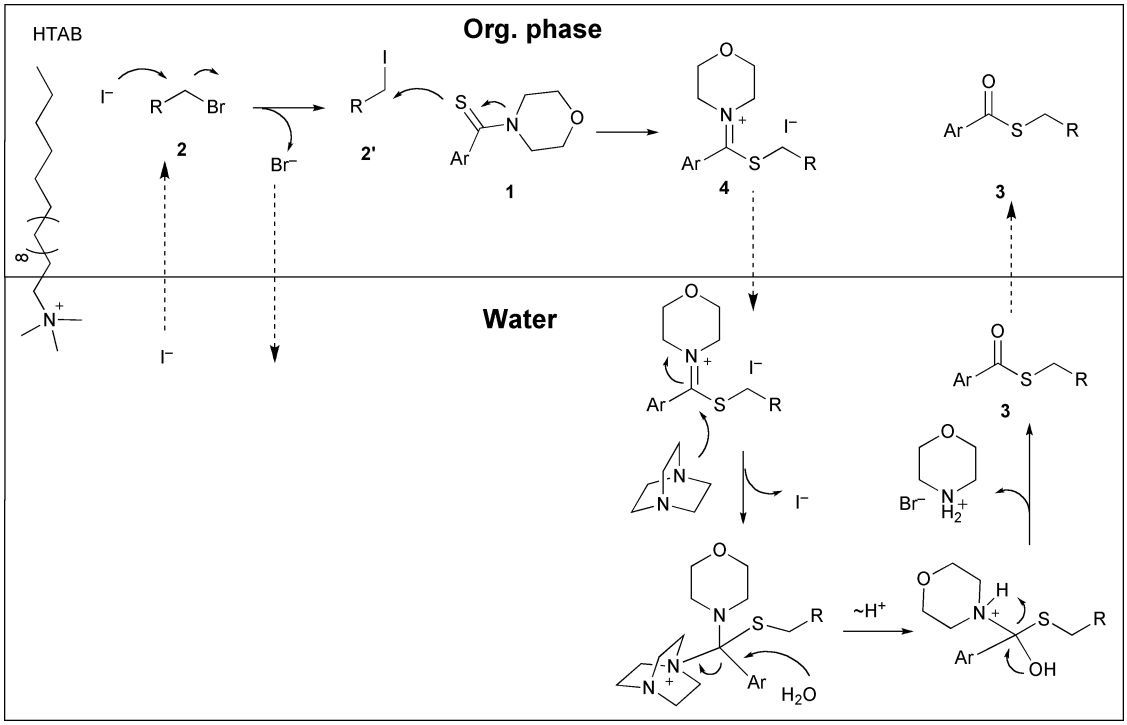
† Electronic supplementary information (ESI) available: Complete experimental procedures, ^{1}H NMR and ^{13}C NMR spectral data (including their copies), and elemental microanalysis for compounds. See DOI: 10.1039/b916852d



Scheme 1

Table 1 Solvent screening in the synthesis of thioesters[a]

Entry	Solvent	Product	Yield (%)
1	CS_2[b]	**3a**	47
2	Dioxane[c]	**3a**	61
3	DMF[b]	**3a**	68
4	2-Propanol[c]	**3a**	77
5	Water[d]	**3a**	72
6	Water/HTAB[d]	**3a**	81
7	Water/HTAB/NaI[d]	**3a**	93

[a] Thioamide (1 mmol), alkyl halide (1 mmol), DABCO (0.22 mmol). [b] In reflux condition, 60 min. [c] At temperature 95 °C, 60 min. [d] At temperature 95 °C, 50 min.

that the reaction course also takes place in water, as well as polar solvents, with a rather good yield (72%). Surprisingly, when catalytic amounts of NaI and a phase-transfer catalyst such as hexadecyltrimethylammonium bromide (HTAB) is added to the reaction mixture, a significant increase in the yield of the reaction is observed (93%). This approach would remove the requirement for the use of organic solvents as reaction media and, consequently, the method is quite eco-friendly.

A variety of substituted phenyl groups were tolerated on thioamides and reacted with various alkyl halides leading to different thioesters. The generality of the method has been demonstrated by the successful synthesis of several thioesters in good to excellent yields (80–96%) and Table 2 summarizes our results.

Our experiments obviously revealed that all kind of alkyl halides (chloride, bromide, and iodide) could be successfully applied in the course of the reaction but better results were obtained with bromomethyl aromatics.

A mechanism is also proposed and shown in Scheme 1. Alkyl halide **2** is first activated by NaI and with the aid of HTAB. Then, thioamide **1** undergoes an *S*-alkylation with the activated alkyl halide **2′** to form thiouronium salt **4** quantitatively and subsequent hydrolysis catalyzed by DABCO affords the corresponding thioesters, **3**.

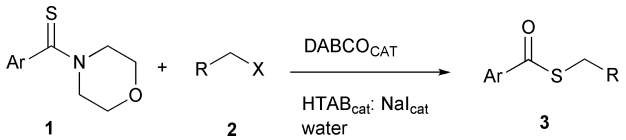
To assess the feasibility of applying this method on a preparative scale, we carried out the reaction of morpholino (4-dimethylaminophenyl) methanethione with benzyl bromide on a 50 mmol scale. As expected, the reaction proceeded smoothly, similar to the smaller scale case (Table 2, entry 5), and the desired *S*-benzyl 4-dimethylaminobenzothioate was obtained in 91% isolated yield.

In addition to the simplicity of the method, high yields, and easy work-up, the salient features of this methodology lie in the fact that the reactions are carried out in aqueous media, in a short time, and in rather mild conditions. Furthermore, purification of the thioester products is achieved with a simple recrystallization in MeOH. Moreover, the method is compatible with many substituents, such as halo, alkoxy, dialkylamino, nitro, *etc.*, in the substrates.

Conclusions

In conclusion, the methodology reported herein is expected to be a quite general route for the synthesis of a wide range of

Table 2 Highly efficient synthesis of thioesters in aqueous media[a]



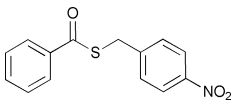
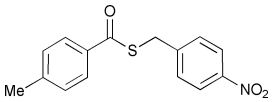
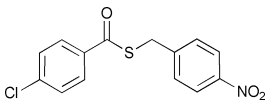
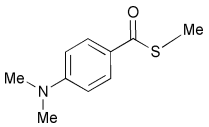
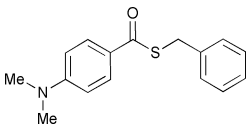
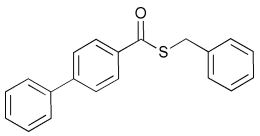
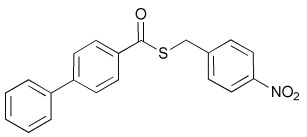
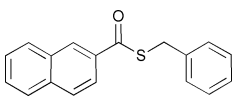
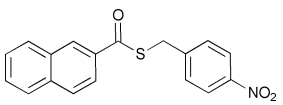
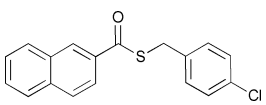
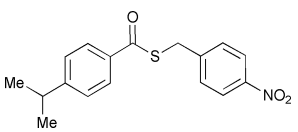
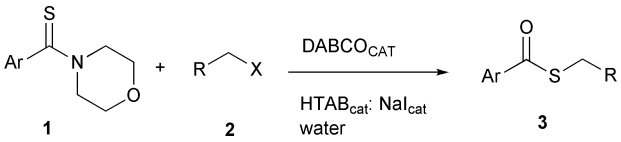
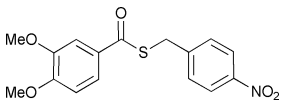
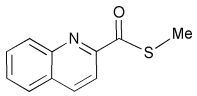
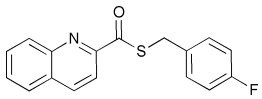
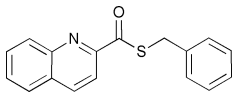
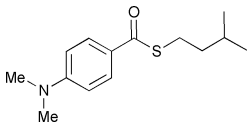
Entry	1	Ar	R	X	Product 3[b]	Yield[c]
1	**a**	Ph	4-Nitrobenzyl	Br		93
2	**b**	4-Tolyl	4-Nitrobenzyl	Br		94
3	**c**	4-Cl-Ph	4-Nitrobenzyl	Br		90
4	**d**	4-Me$_2$N-Ph	Methyl	I		86
5	**d**	4-Me$_2$N-Ph	Benzyl	Br		96
6	**e**	4-Biphenyl	Benzyl	Br		89
7	**e**	4-Biphenyl	4-Nitrobenzyl	Br		91
8	**f**	2-Naphthyl	Benzyl	Br		90
9	**f**	2-Naphthyl	4-Nitrobenzyl	Br		91
10	**f**	2-Naphthyl	4-Chlorobenzyl	Cl		86
11	**g**	4-*i*Pr-Ph	4-Nitrobenzyl	Br		93

Table 2 (*Contd.*)



Entry	1	Ar	R	X	Product 3[b]	Yield[c]
12	**h**	3,4-diMeO-Ph	4-Nitrobenzyl	Br		88
13	**i**	2-Quinolyl	Methyl	I		84
14	**i**	2-Quinolyl	4-Fluorobenzyl	Cl		80
15	**i**	2-Quinolyl	Benzyl	Br		87
16	**d**	4-Me$_2$N-Ph	*iso*-Pentyl	Br		83[d]

[a] Reaction conditions: thioamide derivative (1 mmol), alkyl halide (1 mmol), DABCO (0.22 mmol), HTAB (0.1 mmol), NaI (0.1 mmol), $T = 95$ °C, time = 50 min. [b] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. [c] All yields refer to pure isolated products. [d] Light yellow solid, isolated by flash chromatography (silica gel, EtOAc–Hexane, 1 : 8)

thioesters in water. Apart from being an environmentally benign reaction, the method benefits from the use of cheap and safe starting materials and avoids the use of very unpleasant and noxious thiols, as well as corrosive acid chlorides, in the course of reaction.

Experimental

General procedure for the preparation of thioesters in aqueous media

In a round bottom flask, thioamide (1 mmol), alkyl halide (1 mmol), NaI (0.1 mmol, 15 mg), DABCO (0.22 mmol, 25 mg) and hexadecyltrimethylammonium bromide (HTAB, 0.1 mmol, 36.5 mg) were suspended in water (0.5 ml) with vigorous stirring and heated to 95 °C for 50 min. Then, the reaction mixture was cooled and thereafter an oily residue was left which slowly solidified. After that, the solid was filtered and washed with water (2×10 ml). Finally, the solid compound was recrystallized from MeOH (in some cases with MeOH–$CHCl_3$) to afford pure thioesters as white or pale yellow needles.

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