A facile and practical method for the preparation of thioacetates from alkyl halides and sodium thioacetate catalysed by PEG400

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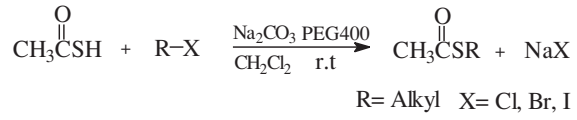
Thioacetates are conveniently prepared in high yields under mild conditions by the reaction of alkyl halides and sodium thioacetate, prepared *in situ* from thioacetic acid and sodium carbonate, catalysed by PEG400 at room temperature.

Keywords: thioacetates, thioacetic acid, alkyl halides, PEG400, sodium carbonate

The roles of thioesters (thiocarboxylic *S*-esters) as versatile synthetic intermediates in organic reactions have attracted a great deal of attention since thioesters possess high reactivity toward various nucleophiles and can be used as acylating agents in acyl transfer reactions or biochemical processes. For example, they can be used in the synthesis of α, β-unsaturated esters and lactones under very mild conditions.[1] Metal enolates derived from thioesters have been employed in asymmetric carbon–carbon bond formation[2] and in the synthesis of macrocyclic natural products.[3] Furthermore, the thioesters can be either oxidized to sulfonic acids[4] or hydrolysed to monothiols.[5]

The most traditional methods for the preparation of thiolesters involve either the coupling of a thiol with a carboxylic acid or an alcohol with a thiolcarboxylic acid. However, it has been found that the former strategy needs long reaction times[6] and the latter needs the participation of dehydrating agents such as DCC,[7] due to the small equilibrium constants. The reaction of alkyl halides with zinc thiolacetate has also been reported as an alternative approach.[1] However, zinc thiolaceate is not readily available and a troublesome procedure has to be performed for its preparation before use. Other methods for thioester synthesis involve cobalt carbonyl-catalysed carbonylation of mercaptans,[8] the cobalt chloride-catalysed coupling of thiols and anhydrides,[9] cleavage of S–S bond by $Sm/CoCl_2$ or $Sm/CoCl_2{\bullet}6H_2O$ system[10] and the use of polymer-supported thiolacetate ion.[11] However, the reagents applied in these methods are not commonly available or are costly. In this respect, a method that involves the use of readily available reagents, such as reaction of alkyl halides and a thiolcarboxylic acid in the presence of a cheap phase-transfer catalyst (PTC) should be interesting and easily be put into industrial production.

It is well known that quaternary ammonium salts, which are predominantly used in liquid–liquid two-phase reactions, and crown ethers, which are in many cases expensive and toxic, are the most commonly used catalysts in phase-transfer reactions. In recent years, polyethylene glycols (PEGs) of various molecular weights have found much industrial application as PTC or solvent promoters in many organic reactions since they can be regarded as acyclic crown ether analogues.[12,13] With a medium molecular weight, PEG400 is a particularly desirable phase-transfer catalyst for non-aqueous heterogeneous reactions. The attractive features of PEG400 include its low cost, stability, ready availability and apparent lack of significant toxicological problems. In addition, compared with crown ethers and quaternary ammonium salts, it has a more powerful ability to solubilise the inorganic salts in non-polar organic solvents such as dichloromethane and benzene due to the fact that it has two terminal polar hydroxyl groups, which play important roles in attacking the crystal lattice of the solids. In continuation of our research on the use of PEGs as PTC,[14,15] we now report a facile method for the preparation of thioacetates by the reaction of alkyl halides and sodium thioacetate, prepared in situ from thioacetic acid and sodium carbonate, catalysed by PEG400 at room temperature. The results are summarised in Table 1.



Scheme 1

In terms of reaction mechanism, the reaction consists of two stages. Thioacetic acid will firstly be neutralised gradually by sodium carbonate to give the thioacetate anion, which will further undergo a substitution reaction with alkyl halides under the catalysis of PEG400 to afford the final products. No additional heat is needed to enhance the reaction rate since the neutralisation reaction at the first stage is exothermic. 5% Excess of thioacetic acid and 10% sodium carbonate over alkyl halides are used in order to ensure the generation of enough thioacetate anion as well as the complete conversion of the substrates. The overdose of 10% of sodium carbonate is used to absorb physically the water formed at the first stage, which will make the separation procedure much simpler as water is filtered off with the solids.

For the sake of comparison, the reaction using benzyl chloride as substrate in the absence of PEG400 was carried out. It was found that the reaction time increased obviously and a yield as low as 15% was obtained, after the reaction was performed at room temperature over 12 hours. However, when 3mol% PEG400 was added, the reaction time was greatly reduced and the yield was increased nearly fourfold (showed in the table, entry 10).

Table 1 Reactions of alkyl halides with sodium thioacetate prepared in situ from thioacetic acid and sodium carbonate catalysed by PEG400 in CH_2Cl_2.

Entry	R–X	Time/h	Yield/%[a]	B.p. (°C/mmHg)	
				Found	Reported[11]
1	n-butyl-Br	3	92	162–164	163–164[1]
2	*n*-butyl-I	2	93		
3	*n*-buty-Cl	6	55		
4	Cyclo-C_6H_{11}-Br	2	85	116–118/50	90–91/15
5	Cyclo-C_6H_{11}-Cl	5	65		
6	*n*-C_8H_{17}-Br	3	88	146–148/50	128–131/24
7	*n*-C_8H_{17}-I	2	90		
8[b]	*t*-butyl-Cl	3	62	128–130	130[1]
9[b]	*t*-butyl-Br	2	60		
10	$C_6H_5CH_2$-Cl	2	93	160–162/50	247–250
11	$C_6H_5CH_2$-Br	1.5	92		
12	$CH_2CH{=}CH_2$-Cl	2	70	125–127	126–128
13	$CH_2CH{=}CH_2$-Br	1.5	75		
14	$C_6H_5COCH_2$-Br	2.5	85	130–132/50	108–110/18
15	Br-$(CH_2)_4$-Br	4	82	158–160/50	120–123/10

[a]Yield of isolated products calculated with reference to alkyl halides.
[b]Iced-water bath was used to lower the reaction temperature.

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Based on the results listed in Table 1, it can be inferred that alkyl iodide is more active than alkyl bromide, which is also more active than alkyl chloride. In fact, the tracing method of GC showed that nearly 40% of *n*-butyl-Cl was unreacted after the reaction was performed for 12 hours. Based on this, we propose that the reaction mechanism for the case from entries 1 to 7 should be S_N2 type since the chloride anion is not a good leaving group, which might account for its longer reaction time and lower reaction rate.

The substrates in entries 8,9,10,11,12 and 13 are more reactive, but high yields were obtained only for benzyl chloride and bromide. We propose that the main reason for the low yields in entries 8 and 9 may be the side reaction of competitive elimination. In order to inhibit the side reaction, more solvent (1.5 times the amount) and an iced-water bath, to keep the temperature low, were used for the reactions in entries 8 and 9. 2-Bromoacetophenone in entry 14 also underwent the reaction smoothly and afforded a desirable yield, and 1,4-dibromobutane in entry 15 could give the double-thioacetated products.

Based on the results of the comparative experiments of several solvents with low boiling points, such as ethyl ether, dichloromethane, acetone and chloroform, we selected dichloromethane as solvent to ensure an excellent separation of the products from the mixture by distillation and good miscibility with PEG400.

In conclusion, we have demonstrated a convenient and efficient method of preparing thioacetates from the corresponding halides catalysed by PEG400. Since the reaction is performed at room temperature, the work up is simple and the solvent should be recyclable. We assume that the method is suitable to be put into industrial application.

Experimental

GC: GC-17A with 2m of column silicon-SE-30 and TLC were used to monitor the reaction process. The solvents were distilled before use. 2-Bromoacetophenone is prepared from acetophenone according to the literature. The remaining substrates, thioacetic acid (98%) and PEG400 are commercially available and were used without further purification.

Typical procedure for the preparation of benzyl thioacetate from benzyl chloride: A mixture of CH_2Cl_2 (20 ml), sodium carbonate (8 g, 0.055 mol), benzyl chloride (12.7 g, 0.1 mol) and PEG400 (1.2 g, 0.003 mol) was stirred in a 100ml three-necked, round-bottomed flask equipped with a magnetic bar. With the dropwise addition of thioacetic acid (8.2 g, 0.105 mol) over a period of about 10 minutes the mixture was stirred at room temperature for 2 hours. The progress of the reaction was monitored by TLC. Upon completion, the solids were filtered and meticulously washed with dried CH_2Cl_2(1–2ml). The filtrate was dried over magnesium sulfate. After CH_2Cl_2 was recovered by distillation from the combined filtrate, benzyl thioacetate 15.5g(93%yield) was collected at 160–162°C/50mmHg by distillation under reduced pressure. The remaining thioacetates were prepared in a similar manner.

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