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Efficient Synthesis of Organic Thioacetates in Water

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Thioacetates as precursors of thiols, are interesting starting point to synthesize other organosulfur compounds. Herein, we propose a simple, efficient and fast method to obtain organic thioacetates using water as a solvent. Taking into account the great attention which has been put on environmentally friendly synthetic procedures in the last decades, we prove the role and the strenght of thioacetate anion as nucleophile for nucleophilic displacement reactions in an aqueous medium. The reactions were carried out under pH control, to prevent the decomposition of mesylate starting materials, using potassium carbonate as a safe and mild base. A simple work up allows to obtain products with eccellent yield and acceptable purity.

Introduction

Organosulfur compounds are an important class of organic molecules, the importance of which is well recognized today for many synthetic purposes. ¹⁻³ These molecules are also studied and manipulated due to the great biological and pharmacological potential, with many positive effects on human health.⁴⁻⁶ Organosulfur compounds are not only important for nutrition,⁷ but they are also building blocks that play key roles in many biological structures and functions and therefore essential for the whole life.^{8,9} Organosulfur chemistry includes a bewildering number of molecules and sulphides, disulphides, sulphonamides, thiosulfinates, isothiocyanates, are just some examples that occur widely in nature.¹⁰⁻¹⁴

One of the common synthetic route to obtain these molecules starts from thiols, ¹⁵⁻¹⁸ which have also, a wide range of application in polymer chemistry, medicinal chemistry, biochemistry and scaffolds chemistry.¹⁹⁻²³ Due to the structural diversity of organosulfur compounds in nature and in numerous biological systems,²⁴⁻²⁷ the development of an alternative and cheap strategy to access these molecules is still attractive.

Organic thioacetates are the most used precursors to these molecules and can be converted to thiols via many strategies. $^{\rm 28-32}$ In the last years many synthetic methods have been discovered. $^{\rm 33-36}$ A

conventional synthesis of thioacetates is carried out through a nucleophilic substitution, starting from organic halides or activated alcohols, using thioacetate anion as nucleophile. Moreover, unsaturated thioacetates, such as alkenyl-thioacetates, are important reagents to obtain the access to unsaturated organosulfur compounds. One of the most important examples of unsaturated organosulfur compounds with great benefits on human health are represented by allium species plants, in which garlic plays an important role.³⁷ Divekar et al. proposed a palladium catalysed synthesis of allylic thioacetates to obtain allylic thiols using thioacetate anion.³⁸

Nevertheless, the classical procedures are characterized by long reaction times, toxic apolar aprotic solvents, and low purity that requires chromatographic techniques with important solvent waste. $^{\rm 39\text{-}41}$ Thus, the development of a simple, rapid and environmentally friendly procedure is very valuable. Potassium thioacetate or thioacetic acid represent the sources of thioacetate anion commonly used, but this nucleophile works well only in conventional solvents, or by anionic activation using silica gel as support.42-45 Traditional procedures are often improved or overcome by green strategies, with the aim to avoid toxic reagents, solvents or purification procedures. 46-49 There are no reported literature methodologies that prove the action and the strength of thioacetate anion in aqueous medium without any catalyst. The role of water has been changing so fast during the past years and applications in chemistry continue to grow incessantly and, as a consequence, it is a perfect candidate to create a green reaction medium.50-5

Here, we report a general synthetic procedure to afford organic thioacetates in aqueous medium, starting from organic mesylates, under pH control. The reaction performed in water, together with the use of a mild base and low temperatures, the absence of any catalyst and of by-products, is a good result to have a mild and environmentally friendly methodology.

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Results and discussion

In our search for a simple and green procedure, the use of organic halides proved to be unfavourable due to the facile hydrolysis of this species in the aqueous system, together with complications related to their toxicity and high environmental impact.^{53,54} Mesylates are a very attractive alternative, especially because in a slightly basic medium these molecules are quite stable in water. Morita and collaborators developed a strategy to convert quantitatively alcohols to mesylates in water at pH near 10.⁵⁵ We used the same system to convert mesylates to thioacetates.

Our aim was to find a synthetic protocol to obtain thioacetates in aqueous medium, with short times, no hazardous reagent, and a simple work up without any further purification. Potassium thioacetate or thioacetic acid can be used as thioacetate source in water (Scheme 1).



R'= allylic, benzylic and propargylic chains

Scheme 1. Nucleophilic displacement of organic mesylates in water by thioacetate anion.

We initiated our investigation starting from benzyl mesylate (**1a**), freshly synthetized almost quantitatively, from benzyl alcohol by a procedure reported in literature.⁵⁶

Our first attempt was to convert the reagent to thioacetates without any use of bases (Table 1, entry 1). The reaction didn't succeed because yield was not satisfactory. Even when the reaction was performed at higher temperatures with increased reaction times and increased amount of potassium thioacetate, the yield was quite low (Table 1, entries 2 and 3). One of the reason for this failure was the instability of methanesulfonates in aqueous acidic medium.

Table 1. Reaction optimization for the synthesis ofbenzylthioacetate from benzylmesylate. a

	Ĉ	OMs -		SAc	
	1a		1b		
Entry	KSAc ^b	K₂CO₃ ^b	Temp. (°C)	Time (hrs)	Yield(%) ^c
1	1.5	0	25	2	20
2	2	0	40	4	35
3	2.5	0	80	5	36
4	1.5	1	25	2	40
5	2	2	40	4	60
6	1.5	3	25	2	75
7	1.5	3	40	2	93
8	2	3	40	2	94

^a The reaction was performed using a round bottom flask equipped with a magnetic stirrer and a reflux condenser. 2 ml of H₂O for 1 mmol of reagent. Either potassium thioacetate or acetic acid can be used.^b Quantities are expressed in equivalents.^c Yield calculated by GC-MS. The addition of K_2CO_3 as a mild base in the reaction mixture enables the formation of the desired product in good yields (Table 1, entries 4-6). The reaction is almost quantitative in two hours at 40 °C using 1.5 equivalents of thioacetate or thioacetic acid and 3 equivalents of base (Table 1, entry 7). The use of a slight excess of thioacetate source is essential for the quantitative outcome. A further increasing amount of thioacetate does not affect the yield of the reaction (Table 1, entry 8).

The use of a mild base is necessary for the pH control of the optimized reaction, to prevent a reversible equilibrium due to the nucleophilic power of water in acidic media.

To demonstrate this statement, we performed a correlation study between pH of the mixture and reaction yield (Table 2). We proved that in a slight alkaline aqueous medium, (pH near 10), the displacement of the mesylate leaving group by thioacetate anion proceeds completely (Table 2, entry 4).

Table 2. Correlation between pH of the mixture and reaction yield. ^a	
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Entry K₂CO₃(M) ^b		pH	۲ield(%) ^د		
1	0.1	8.0	65		
2	0.2	8.5	72		
3	0.3	9.0	84		
4	0.4	9.5	93		
^a This optimization was conducted starting from benzylmesylate					
(1a). The pH of the mixture was measured by pH meter. ^b The					

concentration of potassium carbonate in water was expressed in

molarity.^c Yield calculated by GC-MS.

The use of potassium carbonate is consistent with our purpose. It is a good alternative to regulate pH respect to conventional stronger bases. It is a natural salt, with very low toxicity and safe to handle, so it can play a role in a sustainable procedure as reported by many examples during the past years.^{57,58} We also tried to replace K_2CO_3 with NaOH as a stronger base to reduce the quantity used, but 2 equivalents in any case were necessary to obtain a comparable result with the same pH. With these optimized conditions in hand, we have evaluated the scope of the present method for a variety of allylic substrates, the results are summarized in Table 3.

As expected, allyl mesylate afforded **2b** in 92% yield, final extraction in diethyl ether allows to obtain a quite pure product in almost quantitative yield and without any further purification (Table 3, entry 2).

The starting mesylates are freshly prepared using the conventional procedures and used immediately. A fast and efficient procedure was developed. Benzylic, allylic and propargylic mesylates are easily converted almost totally to thioacetates (Table 3, entries 1, e and 6). Usually these substrates have a borderline behaviour between SN_1 and SN_2 mechanism, but in our study we observed a behavior typical of an SN_2 -type reaction. Allylic groups favours mostly this type of reaction because of the combination with the negatively charged transition state. Erden and coworkers proved by synthetically and computationally studies how strong the SN_2 reaction is accelerated by allylic groups.

In our case, this reaction is also stereospecific with total retention of configuration (Table 3, entries 3 and 4). We proved that the propargylic group is also activating like the allylic groups and the reaction gives the same outcome (Table 3, entry 6).

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^a The reaction was conducted in a round bottom flask equipped with magnetic stirrer and reflux condenser at 40°C. ^b Yield calculated by GC-MS.^c The stereospecificity was determined by ¹H and ¹³C-NMR spectroscopy.

The efficacy of this method was further tested using saturated and unsaturated mesylates without allyl groups in their structure (Scheme 2).



R' = saturated and unsaturated chains

Scheme 2. Nucleophilic displacement reaction of saturated and unsaturated methanesulfonates in aqueous medium.

In Table 4 are summarized the most important attempts to optimize the reaction starting from 5-hexenyl-1-mesylate **1c**. In the absence of potassium carbonate the result was unsatisfactory (Table 4, entries 1- 3).

The reaction yield becomes from good to excellent by raising the temperature and increasing the amount of the base (Table 4, entries 4-8). The use of three equivalents of potassium carbonate allows the reaction mixture to have a pH near 10. The absence of an allyl group in the starting compound allowed us to understand how much the allyl group influences the reaction and to prove that a different unsaturation site does not affect the result.

Table 4. Optimization strategy for the synthesis of 5-hexenylthioacetate $\mathbf{1d}$.^a

OMs				→ ///	SAc
10			1d		
Entry	KSAc ^b	K ₂ CO ₃ ^b	Temp.(°C)	Time (hrs)	Yield(%) ^c
1	1.5	0	25	2	10
2	2	0	40	4	18
3	2.5	0	80	6	24
4	1.5	1	25	2	38
5	2	2	40	4	45
6	2	3	80	6	95
7	1.5	3	80	4	94
8	1.5	3	80	2	93
2					

^a The reaction was performed using a round bottom flask equipped with a magnetic stirrer and a reflux condenser. 2 ml of H₂O for 1 mmol of reagent. Either potassium thioacetate or acetic acid can be used.^b Quantities are expressed in equivalents.^c Yield calculated by GC-MS.

These optimized conditions were used for various saturated and unsaturated mesylates (Table 5). The results demonstrated that the reaction is accelerated by allyl groups, nevertheless, the reaction with non-allyl unsaturated reagents (Table 5, entries 1-3) and saturated reagents (Table 5, entries 4-6), was also suitable to generate the desired products in excellent yields.

The reaction yields are almost the same for both saturated and unsaturated molecules demonstrating that the unsaturation doesn't interfere with this reaction (Table 5).

Entry	Reagent	Product	Yield(%) ^b	
1	OMs	SAc	96	
I	1c	1d	30	
2	OMs	SAc	07	
2	2c	2d	97	
3	OMs SAc		96	
3	Зc	3d	50	
4	() 3 OMs	SAc	95	
	4c	4d		
F	OMs	SAc	96	
5	5c	5d	50	
6	OMs	SAc	07	
σ	6c	6d	97	

 $^{\rm a}$ The reaction was conducted in a round bottom flask equipped with magnetic stirrer and reflux condenser at 80°C. $^{\rm b}$ Yield calculated by GC-MS.

Further investigations were attempted to define if this reaction follows a nucleophilic displacement with first or second kinetic order. Secondary and tertiary mesylates were used to verify if there is a two-step mechanism involving a carbocation formation (Table 6).

There is no nucleophilic displacement on the secondary carbons using the optimized conditions (Table 6, entries 1 and 2). We tried to push the reaction toward the product formation, using a secondary allyl mesylate, but we had no success (Table 6, entry 2). In the case of tertiary carbons, the reaction did not work neither (Table 6, entry 3).

This result is consistent with our hypothesis; in fact, we proved that using secondary and tertiary mesylates as starting compounds the reaction mechanism doesn't proceed through a carbocation formation, thus the reaction follows a SN_2 mechanism instead of SN_1 . Finally, the failure of the reaction observed in the case of phenyl mesylate shows that the only reasonable mechanism is a nucleophilic substitution (Table 6, entry 4). The same reactions performed without base in neutral conditions have the same result, so we can confirm that there are not competitive mechanistic pathways.

 Table 6. Synthesis of secondary, tertiary and phenyl thioacetates.^a



^aAll reactions was conducted in a round bottom flask equipped with magnetic stirrer and reflux condenser at 40°C and 80°C for 2 and 4 hours. 2 ml of H₂O for 1 mmol of reagent. 1.5 mmol of potassium thioacetate or acetic acid have been used.

The correlation between SN_2 reaction and nucleophilic strength is well known and reported.^{60,61} Sulfur is more nucleophilic than oxygen, for this reason we carried out the same reaction on allylic mesylates using acetate anion as a weaker nucleophile instead of thioacetate anion.

This comparison allowed us to define if this reaction is affected or not by nucleophilic strenght. We performed the nucleophilic displacement reaction using acetate anion under the optimized conditions. No substitution of the mesylate leaving group was observed even raising temperature, time and the base (Table 7). These data confirm that the reaction is dependent by the nucleophilic strength. Acetate anion doesn't have the same nucleophilic character in this medium in comparison with others species and no nucleophilic displacement occurs in that direction.

Table 7. Nucleophilic displacement of benzyl-mesylate in aqueous media with acetate anion as the nucleophile.^a

		OMs X	DAc(X=K,H) → H ₂ O		`OAc
Entry	1a KAc ^b	K₂CO₃ ^b	Temp(°C)	1g Time (hrs)	Yield(%)
1	1.5	0	25	2	0
2	2	0	40	4	0
3	2.5	0	80	5	0
4	1.5	1	25	2	0
5	2	2	40	4	0
6	1.5	3	25	2	0
7	1.5	3	40	2	0
8	2	3	40	4	0
a .					

^a The reaction was performed using a round bottom flask equipped with a magnetic stirrer and a reflux condenser. 2 ml of H₂O for 1 mmol of reagent. Either potassium acetate or acetic acid can be used.^b Quantities are expressed in equivalents.

Lastly, we elucidate the role of the water as the solvent for the successful performance of the developed reaction, despite, water is generally excluded for an SN₂ reaction.⁶² Here, we use a slight basic aqueous medium, with different anions in solution, generated from the reagent and the base used. One of the reason why a polar protic solvent is not convenient for a SN₂ reaction is the solvation effect.^{63,64} We proved that water does not affect negatively the reaction but it behaves like a catalyst instead. We used potassium thioacetate or thioacetic acid as a thioacetate sources, that are completely ionized in this basic medium. At the start of the reaction we noticed a particular situation inside the reaction flask. There were many drops in the aqueous mixture that, after completion of the reaction, disappeared and the solution became clear with a distinctive separation of two phases. All the mesylates and the thioacetate derivatives are immiscible in water. Our hypothesis is that the reaction occurs at the aqueous interface with a slight dependence from temperature. Probably thioacetate anion continues to be a strong nucleophile in this medium because the presence of others anions and cations make the water molecules occupied and less available for solvation. We tried to substitute thioacetate anion with other sulfur nucleophiles like thiophenolate anion and other aliphatic thiolate anions but the reaction didn't succeed probably due to a more steric hindrance and a different nucleophilicity of these anions in this reaction medium. Against the conventional procedure, we have an almost quantitative, fast and at the same time green reaction that avoid the use of the classical polar aprotic solvents like DMF or DMSO.

Conclusions

We developed a simple, mild and efficient procedure to convert organic mesylates to thioacetates. The reaction apparatus is simple and all reagents are safe to handle. Potassium carbonate as a pH controller is a green alternative to strong bases. We proved by different experiments that this nucleophilic displacement reaction follows a SN₂ type mechanism. Despite the classical SN₂ procedure,

no toxic solvents were used. This procedure in water is a valid alternative to conventional methods and a suitable access to the synthesis of different types of thiols and of course an efficient starting point for the synthesis of more complex organosulfur compounds.

Conflict of interest

There are no conflicts of interest to declare.

Experimental section

General

Commercially available reagents were purchased from Sigma-Aldrich Chemical Co. (Milano, Italy) and used as supplied unless stated otherwise. All reactions were carried out in atmospheric conditions. ¹H NMR spectra were recorded at 300 MHz, while ¹³C NMR spectra were measured at 75 MHz. Spectral analysis was performed at 293 K on diluted solutions of each compound by using $CDCl_3$ as the solvent. Chemical shifts (δ) are reported in ppm and referenced to CDCl₃ (7.25 ppm for 1 H and 77.0 ppm for 13 C spectra). Coupling costants (J) are reported in Hertz (Hz). Reaction mixtures were monitored by thin layer chromatography (TLC) using Merck Silica gel 60 F₂₅₄ precoated aluminium sheets or Merck Aluminium oxide 60 F_{254} neutral precoated alluminium sheets, UV light (254 nm), iodine or diluted solution of H_2SO_4 for the detection. Evaporation of solvents was performed at reduced pressure using a rotary vacuum evaporator. The GC-MS Shimadzu workstation is constituted by a GC 2010 (provided of a 30 m-QUADREX 007-5MS capillary column, operating in "split" mode, 1 ml min⁻¹ flow of He as carrier gas) and a 2010 quadrupole mass-detector.

General procedure for the synthesis of organic mesylates (1a-6a, 1c-6c, 1e-4e).

All the mesylates were synthetized starting from the corresponding alcohol following the same procedures reported in literature.^{56,65-67} The reactions were almost quantitative after work up and the freshly prepared products were used directly for the next step. All GC-MS and NMR spectra were comparable to those reported in literature, ^{52,61-63} while, for the new derivatives, spectroscopic data are reported in the Supporting Informations.

In a one neck round bottom flask, 4.6 mmol of alcohol were 10 dissolved in 20 ml of CH_2Cl_2 and the mixture cooled down at 0 °C. 4.6 mmol of triethylamine were added under stirring and then 4.6 11 mmol of mesyl chloride were added dropwise under stirring. The mixture was stirred for one hour and half. After that, the reaction was quenched with 2 ml of HCl 1N and the solution washed with NaHCO₃ saturated aqueous solution. The organic phase was extracted, washed three times with water and dried over Na₂SO₄. The solvent was removed under vacuum to obtain a pink liquid in 13 an almost quantitative yield (GC-MS).

General procedure for the synthesis of benzyl thioacetate (1b), allyl thioacetates (2b-5b) and propargyl thioacetate (6b).

 $2.7\ \text{mmol}$ of freshly prepared mesylate were put in a one neck round bottom flask. In the same flask 20 ml of 0.4 M aqueous

potassium carbonate solution were added. 1.5 eq of potassium thioacetate or acetic acid were added dropwise to the solution under stirring. The mixture was stirred at 40 °C with a reflux condenser for almost 2 hours. The organic phase was extracted with a small portion of diethyl ether and washed three times with water. The organic phase was dried over Na₂SO₄ and the solvent removed under vacuum. The product was recovered as a yellow liquid in an almost quantitative yield (GC-MS).

General procedure for the synthesis of primary thioacetates (1d-6d)

2.8 mmol of freshly prepared mesylate were put in a one neck round bottom flask. In the same flask 20 ml of 0.4 M aqueous potassium carbonate solution were added. 1.5 eq of potassium thioacetate or acetic acid were added to the solution under stirring. The mixture was stirred at 80 °C under reflux for almost 2 hours. The organic phase was extracted with a small portion of diethyl ether and washed three times with water. The organic phase was dried over Na₂SO₄ and the solvent removed under vacuum. The product was recovered as a yellow liquid in an almost quantitative yield (GC-MS).

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