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A General and Mild Synthesis of Thioesters and Thiols from Halides

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Summary: The conversion of a wide variety of halides to thioesters by reaction with potassium thiocetate under mild conditions is described, and the generality of the method is demonstrated.

Thiols and their derivatives are important functional groups in organic synthesis,[1-5] and they are also present in many biologically active compounds.[6] The most common starting materials for preparing sulfur-containing molecules are halides, alcohols, and their derivatives.[2,3,5] Reliable methods for their conversions to thiols and derivatives are known.[1-5] In view of the complex and sensitive nature of many target molecules synthesized today, mild and high-yield synthetic routes to thiols are desirable. Potassium thioacetate (KSAc) is a popular reagent for the above conversions via the intermediacy of thioesters, which can be easily isolated if desired.[1,2] However, most literature methods involved the reaction of halides or equivalents with KSAc in refluxing solvents such as ethanol,[7] acetone, [7a,8] THF,[9] or DMF,[10] and yields are often not high. A few mild reactions have been reported with activated precursors such as halo-carbonyl compounds[11] and allylic compounds.[12] A few reports describing such mild reactions with other halides and related compounds have appeared,[13] and a systematic survey of halides to establish the scope of the reaction is lacking. Considering the high nucleophilicity of KSAc and the usefulness of the conversion, we carried out a study using a wide variety of organic halides. Here we wish to report that by using dipolar aprotic solvents such as DMF, the reactions can be conveniently run at room temperature. Many halides also react efficiently with KSAc in acetone or MeOH, thus simplifying purification. Using known procedures, thiols can be obtained from thioesters in high yields.[7a, 8b, 9, 10a, 12b, 13-19]

Table I summarizes the results of the reactions carried out in DMF. DMSO can also be used as reaction solvent but the removal of solvent from the product is more difficult. Typical experimental procedures are as follows: halide (1.0 mmol) was added to a stirred solution of potassium thiocetate (1.0 mmol) in DMF (20 mL), and the mixture was left stirring at room temperature for an appropriate time. The solution was then partitioned between H_2O and CH_2Cl_2 (3x), and the combined organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The reaction products were identified by ^1H and ^{13}C NMR spectroscopy, microanalysis or mass spectrometry, and physical properties were compared with literature values where available. From Table I, it is evident that aliphatic bromides and chlorides react readily with KSAc in DMF to afford the corresponding thioesters in high yield.

Table II summarizes the results of the reactions of halides and other substrates with KSAc in acetone. As with DMF solvent, the reaction conditions were not optimized. Inspection of Table II reveals that primary bromides (entries 5-

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Table I. Synthesis of thioesters from halides in DMF [a,b]

Substrate	Time (h)	Yield (%)	Substrate	Time (h)	Yield (%)
$Cl(CH_2)_7CH_3$	96	84	$Br(CH_2)_2CN$	3	96
$Cl(CH_2)_3CH(OCH_2CH_2O)$	72	92	$Br(CH_2)_2CH(OCH_2CH_2O)$	46	86
$Br(CH_2)_7CH_3$	17	88	$BrCH_2(OCH_2CH_2O)$	67	77
$Br(CH_2)_2Ph$	16	92			

a. No attempt was made to optimize the reaction conditions.
b. In general, there is a small amount of unreacted halides in the products, especially when the halides are chlorides, presumably due to the formation of potassium halide precipitates. However, the use of slight excess of KSAc and efficient stirring eliminates this problem.

12, 14, 15) and iodides (entries 16, 22) secondary bromides (entry 13), and activated halides such as benzylic (entries 3, 18) allylic (entry 17), and halocarbonyl compounds (entries 4, 19-21) all afford good yields of the desired products. The reactions are compatible with many functionalities. 3-Bromocamphor showed no reaction, while $Br(CH_2)_3NH_2 \cdot HBr$ gave complex mixtures.

Reactions with primary chlorides in acetone do not go to completion, so the DMF procedure described earlier should be used. The lower reactivity of chlorides can be used to selectively convert primary iodides (entry 16) and bromides (entry 15) to thioesters while the chlorides in the molecules remain intact. The reactivity of secondary bromides is lower than primary ones, and entry 14 shows that selective conversion of the latter to thioester is possible. Mesylates also react well with KSAc to give desired products. Ethyl acrylate undergoes clean conjugate addition with KSAc. From Table II, it is clear that unhindered bromides and iodides as well as activated halides in general react with KSAc readily in acetone or methanol at room temperature to give thioesters in high yield. This reaction provides one of the most convenient methods of preparing thioesters and hence thiols from halides.

The conversions of thioesters to thiols can be readily accomplished by using aqueous NaOH/acetone or aqueous NaOH/methanol at room temperature followed by neutralization and extraction. For example, thioesters from 1.0 mmol halide reactions dissolved in acetone (10ml) were treated with 3M aqueous NaOH (10 mL) for 1-2 h. The solution was then neutralized with 1 M HCl to pH 7, extracted with CH_2Cl_2 (3x), dried, and evaporated to give thiols in good yields (80-95%). Other methods of converting thioesters to thiols are known, such as treatment with NaOMe/MeOH,[8b,9,14] LiOH,[10a] K_2CO_3/DMF,[12b] NH_4HCO_3,[15] $LiAlH_4$/THF, [12a,16] Pd acetate/borohydride resin,[17] and $LiAlH_4/Et_2O$.[13a,18] Recently, NaSMe/MeOH has been described as a mild, selective method for deprotection of thioacetates.[19] Thioesters have also been prepared by reaction of AcSH/$ZrCl_4$ with O-silylated hexopyranoses.[20]

In summary, we demonstrated that the conversion of halides to thioesters and thiols can be achieved under mild conditions, and the reactions are rather general for many halides and related derivatives. This simple and high-yield procedure is often preferable to alternatives such as those involving NaHS, Na_2S, and thiourea.

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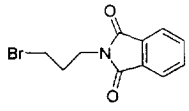
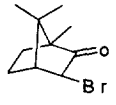
Table II. Synthesis of thioesters from halides and other derivatives in acetone[a,b,c]

entry	substrate	product	time (h)	yield (%)
1	$Cl(CH_2)_7CH_3$	thioester	24	64
2	$Cl(CH_2)_7CH_3$	thioester	63	42[d]
3	$ClCH_2Ph$	thioester	17	94
4	$CH_3CHClCOCH_3$	thioester	20	95
5	$Br(CH_2)_9CH_3$	thioester	26	92
6	$Br(CH_2)_9CH_3$	thioester	69	88[e]
7	$Br(CH_2)_3OH$	thioester	14	91
8	$BrCH_2CH_2OMe$	thioester	40	94
9	$BrCH_2CH_2Br$	bis (thioester)	24	92
10	$Br(CH_2)_4COOEt$	thioester	40	96
11	$BrCH_2CH_2COOH$	thioester	7	93
12		thioester	25	90
13	$CH_3CH_2CHBrCH_3$	thioester	66	86
14	$Br(CH_2)_3CHBrCH_3$	$AcS(CH_2)_3CHBrCH_3$	21	88
15	$BrCH_2CHMeCH_2Cl$	$AcSCH_2CHMeCH_2Cl$	24	89
16	$I(CH_2)_3Cl$	$AcSCH_2CH_2CH_2Cl$	22	92
17	$CH_2=CHCH_2Br$	thioester	18	90
18	$PhCHBrCH_3$	thioester	24	91
19	$PhCOCH_2Br$	thioester	17	96
20	$Me(CH_2)_3CHBrCOOH$	thioester	9	92
21		thioester	22	93
22	$I(CH_2)_6CH_3$	thioester	24	94
23	$MeO_2SO(CH_2)_4OSO_2Me$	bis (thioester)	70	82
24	$CH_2=CHCOOEt$	$AcSCH_2CH_2COOEt$	52	87
25		No reaction	54	
26	$Br(CH_2)_3NH_2 \cdot HBr$	complex mixture	28	

a. The products were characterized by ^1H and ^{13}C NMR spectroscopy, mass spectrometry or elemental analysis, and physical properties were compared to literature values where available.
b. No attempt was made to optimize the reaction conditions.
c. The extracted products generally contain small amount of the starting material but it can be eliminated through efficient stirring and use of excess KSAc.
d. The reaction was run in acetonitrile under the same conditions.
e. The reaction was run in methanol under the same conditions.

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