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NUCLEOPHILIC SUBSTITUTION OF S_N1-ACTIVE HALIDES USING ZINC SALTS: PREPARATION OF THIOLACETATES

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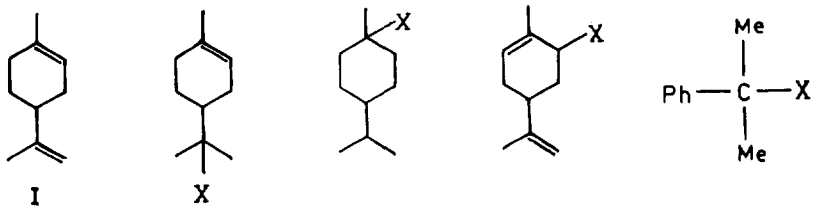
Abstract - Tertiary alkyl, allylic and benzylic halides react with zinc thiolacetate, prepared *in situ*, under optimised conditions to yield the corresponding thiolacetates in moderate to good yields.

Thiolesters (thiocarboxylic S-esters) are well recognised as acylating agents in biochemical processes and acyl tranfer reactions in organic synthesis. Because of their high reactivity towards various nucleophiles, they have attracted a great deal of attention as versatile synthetic intermediates in a variety of chemical transformations. Mention may be made of their application in the synthesis of α, ß-unsaturated esters and lactones under very mild conditions[1]. Metal enolates derived from thiolesters have been employed in the synthesis of macrocyclic natural products[2] and in the asymmetric carbon-carbon bond formation[3]. Further, thiolester group is a relatively stable moiety which affords thiol on saponification or reduction with $LiAlH_4$.

The most general strategies for the preparation of thiolesters involve either coupling of thiol with a carboxylic acid (or an equivalent group)[4] or an alcohol with thiolcarboxylic acid. The latter strategy is illustrated by an efficient and stereoselective conversion of alcohols to thiolesters by a modification of PPh_3-dialkyl azodicarboxylate inversion procedure[5]. Other general methods involve either the initial activation of carboxylic acid[6] or alcohol[7]. The simplest procedure for the preparation of thiolesters consists of treating alkyl halides with alkali metal salts of thiolcarboxylic acids in polar solvents[8]. But the yields are generally low with secondary halides and they further drop in case of tertiary halides, due to competitive elimination.

That S_N1-active halides could be efficiently substituted with zinc salts of nucleophiles has been demonstrated by the synthesis of alcohols, ethers and esters[9,10], thioethers and thiolesters[11], azides[12] and thiocyanates[13]. In case of thioethers and thiolacetates, the reaction is shown to be applicable to primary and secondary alkyl halides as well and explained as due to their superior nucleophilicity. Another attractive route reported for a wide range of thiolesters proceeds through the condensation of benzylic, allylic and tertiary alcohols with thiolacids in presence of stoichiometric amount of zinc iodide[14]. Interestingly, under these conditions, primary and secondary alcohols afford O-esters instead. On the whole, these two methods may be considered as alternative approaches, differing only in the method of preparation of the zinc salts. However, we found that both these methods were ineffective to yield *p*-menth-1-ene-8-thiolacetate (fig.1, III) from the corresponding chloride or alcohol. Incidentally, we envisaged this as a step in the synthesis of *p*-menth-1-en-8-thiol (IV), a flavour-impact constituent of grapefruit juice aroma (threshold value $<10^{-4}$ ppb in water)[15].



I	X			
X = Cl	II	V	VII	IX
X = SAc	III	VI	VIII	X
X = SH	IV			

FIG 1. NEW THIOLACETATES (THIOLS) FROM THE CORRESPONDING HALIDES

8-Chloro-*p*-menth-1-ene (II), a sterically crowded and labile tertiary halide, was obtained in near quantitative yields by the addition of HCl to *p*-mentha-1,8-diene (I) under controlled conditions. Zinc thiolacetate was prepared by the earlier procedure[11] of contacting ZnO or $ZnCO_3$ with AcSH in C_6H_6 followed by removal of water formed in the reaction by azeotropic distillation. The resultant deep red salt was stirred with II in C_6H_6 in presence of pyridine. But II remained unreacted even after prolonged refluxing. On the other hand, in the absence of pyridine, the reaction proceeded to give mainly elimination products. These observations prompted us to re-examine the reaction.

Zinc thiolacetate apparently is a sensitive reagent, susceptible to thermal decomposition. Hence, it needs to be prepared under mild conditions and handled carefully in the subsequent substitution reaction. Two alternative methods of salt preparation were standardised (see experimental) and the efficacy of salts evaluated by carrying out the reaction with *t*-BuBr. They both afforded *t*-BuSAc in high yields (table 1, entry 2) but differed in their reactivity towards II. The salt *ex* method A gave the thiolacetate (III) in 40% yield (entry 11), whereas the salt *ex* method B yielded a mixture of thiolacetates, arising from both substitution of the halide and addition of free AcSH across the double bond. In case of 1-chloro-*p*-menthane (V), another highly sterically crowded tertiary halide, the former gave low yields of VI, but the latter afforded it in 70% yield (entry 12). Interestingly, HX and H_2S produced in this process did not affect either the substrate or the product. In fact, the zinc salt *ex* method B worked exceptionally well with several other saturated tertiary alkyl halides. However, zinc thiolacetate *ex* method A was generally applicable to all S_N1-active halides (table 1).

Zinc thiolacetate prepared by either of the methods did not yield the substitution products with primary and secondary halides. As expected, bromides reacted faster than the corresponding chlorides. The reaction accelerated with the increase in degree of substitution in allylic and benzylic substrates. Also, an allylic substrate underwent substitution attended with rearrangement to give the thermodynamically more stable product (entry 9). Racemisation of the product was observed in case of an optically active allylic halide, VII (entry 10). All these observations were in conformity with the earlier findings concerning oxygen nucleophiles and supported the intermediacy of ion-quadruplet[9,10]. Zinc halide, a Lewis acid formed in the reaction, adversely affects both substrate and product. It is normally scavenged with an organic base (pyridine). However, in the present reaction, the sulphur nucleophile itself complexed with the base and was no longer available for the substitution (see experimental). In the absence of base, the zinc halide preferentially complexed with the remaining zinc thiolacetate, rendering the reaction incomplete. Therefore, the latter had to be employed in twice the stoichiometric quantities.

We describe here a simple and efficient method of preparing benzylic, allylic and tertiary alkyl thiolacetates from the corresponding halides. This is a synthetically attractive route, especially for tertiary alkyl thiols, which are not easily accessible by direct mercaptanation of the corresponding alcohols or olefins[8].

EXPERIMENTAL

GC analyses were carried out on 6' X 1/8" (O.D) SS columns having 10% OV-101 or carbowax 20M on Chromosorb W. ^{1}H-NMR spectra (values) were recorded on a 90 MHz instrument in CCl_4 using TMS as the internal standard. Simple alkyl halides were either procured commercially or prepared by the standard procedures[16]. II[9], V[9], VII[17] ($[\alpha]_D^{20}$ = -225°) and IX[18] were prepared by the reported methods. AcSH (`Aldrich') was distilled (b.p. 76-78°C) and commercial $ZnCl_2$ and ZnS were freshly fused/calcined. Purity and chemical identity of the thiolacetates were ascertained by analysis on HP 5995 B GC-MS instrument [EI 70 eV, He 1 ml/min, HP-101 fused silica cap. column (25 m x 0.2 mm x 0.3 um)]. Also, the presence of -$SCOCH_3$ group in them was confirmed by IR (strong band at 1684-90 cm^{-1}) and NMR (singlet at 2.30, 3H). Yields, b.p.s (uncorrected), ^{1}H NMR and MS data of the products are given in table 1.

Preparation of zinc thiolacetate

Method A: AcSH (3.04 g, 40 mmol) was added to a solution of $ZnCl_2$ (2.72 g, 20mmol) in dry acetone (25 ml) in the presence of K_2CO_3 (2.76 g, 20 mmol) at 0°C and stirred for 15 min. The mixture was further stirred at room temperature for 30 min and then the solvent removed in a flash evaporator. The residue was vacuum-dried over KOH pellets for 12 h.
Method B: AcSH (3.04 g, 40 mmol) and ZnS (1.92 g, 20 mmol) were stirred together for 2 h in CH_2Cl_2 (30 ml) at ambient temperature.

Reactions of *t*-BuBr with zinc thiolacetate:

a) The reaction mixture consisting of *t*-BuBr (20 mmol) and $Zn(SAc)_2$ (20 mmol, prepared by method A or B), in CH_2Cl_2 (25 ml) was stirred under reflux. Progress of the reaction was monitored by ^{1}H NMR, looking for the disappearance of the signal at 1.82 and appearance of a new signal at 1.43. The reaction mixture was worked up by adding 2N HCl (50 ml) and separating the organic layer. The latter was washed free of acid, dried and concentrated. Distillation of the residue using a Vigreux column afforded pure *t*-BuSAc.

b) To the above reaction mixture, pyridine (20 mmol) was added and the mixture stirred under reflux. Even after 48 h, no *t*-BuSAc was detected by ^{1}H NMR and the unreacted halide was recovered, after work-up.

Preparation of thiolacetates

General procedure: To $Zn(SAc)_2$ (20 mmol) in CH_2Cl_2 (60 ml), halide (20 mmol) was added and the reaction mixture stirred under reflux. Progress of the reaction was monitored either by TLC or GC for the disappearance of the

Table 1: **Reaction of alkyl halide (RX, 20 mmol) with $Zn(SAc)_2$[a] (20 mmol) in CH_2Cl_2**

No.	RX	RSAc				
		Time h	Yield[b] %	B.P °C/Torr	^1H NMR	MS(m/z)
1.	t-BuCl	48 (16)*	76 (87)*	130/760	1.46(9H,s), 2.26(3H,s)	
2.	t-BuBr	8 (12)*	75 (82)*	"		
3.	t-AmCl	20 (14)*	45 (80)*	62/30	0.90(3H,t,J=1Hz), 1.40 (6H,s), 1.75(2H,q, J=1Hz), 2.20(3H,s)	
4.	BzCl	36	85	90/0.6	2.30(3H,s), 4.10(2H,s), 7.33(5H,s)	
5.	BzBr	20	81	"		
6.	α-Ph-EtCl	20 (12)*	78 (65)*	132/5.0	1.60(3H,d,J=6Hz), 2.23 (3H,s), 4.70(1H,q, J=6Hz), 7.3(5H,br)	
7.	IX	20 (10)*	45 (72)*	96/1.0	1.83(6H,s), 2.13(3H,s), 7.06-7.60(5H,br)	194(5), 151(2), 119(95), 103(45), 91(100), 77(50), 56(54), 43(62), 41(57).
8.	Allyl Br	14	86	59/19	2.33(3H,s), 3.16(2H,d, J=1Hz), 4.96-5.36(2H, m), 5.50-5.96(1H,m)	
9.	1,1-Me_2 Allyl Cl	7	89[c]	72/15	1.66(6H,s), 2.26(3H,s), 3.43(2H,d,J=9Hz), 5.16(1H,m)	
10.	VII	2	75[d]	110/0.8	1.70(3H,s), 1.73(3H,s), 1.80-2.20(5H,br), 2.30 (3H,s), 4.13(1H,br), 4.73(2H,s), 5.56(1H,br)	210(2), 168(21), 167(39), 134(75), 119(92),107(43), 105(40), 93(84), 91(100), 76(42), 43(65), 41(45).
11.	II	20	40[e]	100/1.0	1.45(3H,s), 1.50(3H,s), 1.63(3H,s), 1.80-2.16 (7H,br), 2.21(3H,s), 5.36(1H,br)	212(2), 169(34), 136(24), 121(37), 95(28), 93(54), 67(23), 53(22), 43(100), 41(57).
12.	V	48 (24)*	10 (70)*[f]	90/0.8	0.73 & 0.86(6H), 1.06-1.53(10H,br), 1.56 (3H,s), 2.26(3H,s)	214(1), 171(1), 138(60), 123(16), 95(100), 83(90), 67(64), 55(62), 43(86).

a. *ex* Method A, unless otherwise stated; b. Recovered yield; c. 3,3-Me_2 allyl SAc
d. Optically inactive, 1:9 *cis/trans* mixture (GC); e. 40 mmol of $Zn(SAc)_2$ was used;
f. 3:1 *cis/trans* mixture; *. pertain to reactions with the salt *ex* method B

halide. The salts were filtered off and the filtrate was successively washed with 2N HCl, sat. aq. $NaHCO_3$, and water, dried and concentrated. The crude product was either distilled or chromatographed over SiO_2 (100-200 mesh) using hexane-EtOAc mixtures to get pure thiolacetate.

REFERENCES

1. Masamune,S; Kamata,S; Schilling,W. *J.Am.Chem.Soc.* **1975,** *97,* 3515.

2a. Nicolaou,K.C. *Tetrahedron* **1977**, *33*, 683.

b. Masamune,S; Bates,G.S; Corcoran,J.W. *Angew.Chem.Int. Ed.(Eng.)* **1977**, *16*, 585.

3. Hirama,M; Garvey,D.S; Lu,L.D.-L; Masamune,S. *Tetrahedron Lett.* **1979,** 3937.

4. Ahmad,S; Iqbal,J. *Tetrahedron Lett.* **1986**, 3791 and references cited therein.

5. Volante,R.P. *Tetrahedron Lett.* **1981**, 3119.

6. Liu,H.J; Sabesan,S.I. *Can.J.Chem.* **1980** *58*, 2645 (1980) and references cited therein.

7. Swann,D.A; Turnbull,J.H. *Tetrahedron* **1968**, *24*, 1441.

8. Wardell,J.L. in *The Chemistry of the Thiol Group* **1974** (ed. S.Patai), John Wiley, Part 1, New York pp.163.

9. Gurudutt,K.N; Ravindranath,B; Srinivas,P. *Tetrahedron* **1982**, *38*, 1843.

10. Ravindranath,B; Srinivas,P. *Tetrahedron* **1984**, *40*, 1623.

11. Rajanikanth,B; Ravindranath,B. *Ind.J.Chem.* **1984**, *23B*, 1043.

12. Ravindranath,B; Srinivas,P. *Ind.J.Chem.* **1985**, *24B*, 1178.

13. Gurudutt,K.N; Sanjay Rao; Srinivas,P. *Ind.J.Chem.* **1991**, *30B*, 345.

14. Gauthier,J.Y; Bourdon,F; Young,R.N. *Tetrahedron Lett.* **1986**, 15.

15. Demole,E; Enggist,P; Ohloff,G. *Helv.Chim.Acta.* **1982**, *65*, 1785.

16. Vogel,A.I. *A Text Book of Practical Organic Chemistry* **1989**, 5th ed. (Longmans Green, London).

17. Ravindranath,B; Srinivas,P. *Tetrahedron* **1983**, *39*, 3991.

18. Gurudutt,K.N; Jagan Mohan Rao,L; Sanjay Rao; Srinivas,P. *Ind.J. Chem.* **1993**, *32B*, 468.

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