Tetrahedron Letters,Vol.27,No.32,pp 3791-3794,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

COBALT(II) CHLORIDE CATALYSED COUPLING OF THIOLS AND ANHYDRIDES: A NEW AND EFFICIENT SYNTHESIS OF THIOL ESTERS

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Summary: Cobalt(II) chloride in acetonitrile catalyses the coupling of anhydrides or acid chlorides with thiols to yield thiol esters in excellent yields.

The role of thiol esters (thio-carboxylic S-esters) as acylating agents in biochemical processes and their high reactivity with various nucleophiles, has made them an attractive synthetic intermediate in a variety of chemical transformations. Lately, their use in the lactonisation processes[1] involved in the synthesis of macrocyclic natural products and the asymmetric carbon-carbon bond formation[2] achieved through the metal enolates derived from thiol esters, has added a new dimension to the utility of these esters. The increasing need for an easy access to the thiol esters has in past, culminated into the development of various novel synthetic methods for their preparation[3-16]. Recently two attractive methods for conversion of alcohols and thiol acids to thiol esters have been reported[17]

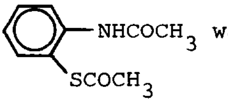
Imamoto and coworkers[16] have efficiently coupled thiols with carboxylic acids in the presence of polyphosphoric esters. This method seems very attractive but longer reaction period imposes some limitation on its utility. Thiols and acyl chlorides have been converted into thiol esters by earlier workers where they first convert thiols into thallium[3], tin[13] or copper[8] mercaptides followed by the coupling with the acid chlorides. These methods have some limitations in the sense that a prior conversion of thiols to mercaptides becomes mandatory which certainly limits the scope of these reactions particularly in case where the handling of toxic thallium compound are involved. We have tried to overcome these deficiencies in the existing methodology and disclose here an efficient way to these thiol esters by a direct coupling between thiols and anhydrides or acid chlorides.

We discovered that when a catalytic amount of anhydrous $Co^{II}Cl_2$ was dissolved in acetonitrile and stirred with a mixture of an anhydride or acid chloride and a thiol at the room temperature for 30 min. to 2 hrs, excellent yields of thiol esters were obtained (Table):

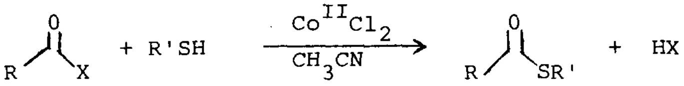
TABLE : Synthesis of Thiol Esters

$$\text{R-CO-X} + \text{R'SH} \xrightarrow[\substack{CH_3CN \\ 20^{o}C}]{Co^{II}Cl_2} \text{RCO-SR'} + \text{XH}$$

Entry	R'	R	X	Time(h)	Yield[a,b] (%)
1.	C_6H_5	CH_3	$OCOCH_3$	1.5	96
2.	C_6H_5	CH_3	Cl	0.5	95
3.	C_6H_5	C_6H_5	Cl	1.0	80
4.	C_6H_5	CH_3CH_2	$OCOCH_2CH_3$	1.5	91
5.	C_6H_5	CH_3CH_2	Cl	0.5	90
6.	C_6H_5	$CH_3CH_2CH_2$	$OCOCH_2CH_2CH_3$	2.0	85
7.	C_6H_5	$CH_3CH_2CH_2$	Cl	1.0	80
8.	p-Br-C_6H_4-	CH_3	$OCOCH_3$	1.5	95
9.	p-Br-C_6H_4-	CH_3	Cl	0.5	90
10.	C_6H_5-CH_2-	CH_3	$OCOCH_3$	2.0	89
11.	C_6H_5-CH_2-	$CH_3CH_2CH_2$-	$OCOCH_2CH_2CH_3$	1.0	91
12.	HS-CH_2-CH_2-	CH_3	$OCOCH_3$[c]	2.0	94
13.		CH_3	Cl[c]	1.0	89
14.	p-CH_3-C_6H_4-	CH_3	$OCOCH_3$	1.5	92
15.		$CH_3CH_2CH_2$	$OCOCH_2CH_2CH_3$	2.0	80
16.	O-NH_2-C_6H_4-	CH_3	$OCOCH_3$[c,d]	2.0	81
17.	HS-$(CH_2)_3$-	CH_3	$OCOCH_3$[c]	2.0	80
18.	CH_3-CH-COOH	CH_3	$OCOCH_3$	2.0	70

a) yields are based on thiols; b) all the products were properly characterised by ^1H NMR and IR; c) two equivalent of the acylating reagent were used and only the diacylated product were formed; d) 

was the only product formed.



Typically, anhydrous cobalt(II) chloride (≃ 50 mg) is dissolved in dry acetonitrile and a mixture of anhydride or acid chloride (1.1 equiv.) and thiol (1 equiv.) in dry acetonitrile is added slowly over a period of 5 min. at room temperature. The resulting mixture is stirred at ambient temperature under a atmosphere of nitrogen for the time indicated in the table. Acetonitrile is evaporated on a rotary evaporator and the residue is dissolved in diethyl ether. The ether layer washed successively with saturated solution of sodium bicarbonate and water after drying and evaporation of ether the product is isolated by column chromatography. In some cases the products were quite pure and did not require any chromatographic separation.

The method is suitable for the anhydrides and acyl chlorides with the later being slightly more reactive than the former. A variety of thiols undergo this reaction with comparable reactivity and in case of O-aminothiophenol and 1,2 and 1,3-dithiol two equivalents of anhydrides or chlorides were used, which resulted in complete formation of the diacylated products in very high yields (entry 12, 16 and 17 in Table). A carboxylic function is also compatible under these reaction conditions as evidenced by the conversion of 2-mercaptopropionic acid to the S-acylated product (entry 18).

In the reactions where acid chlorides are used as acylating reagents, one equivalent of HCl is generated but we have observed that it has no detrimental effect on the outcome and the yield of these reactions. However, the validity of these reactions involving acid sensitive substrate remains to be tested. Since the reactivity of acid chlorides and anhydride are marginally different in these reaction, the reaction involving anhydrides, which generates a mild acid under these conditions, is the preferred method for effecting this type of coupling.

Mechanistic studies are underway in our laboratory to assess the role of cobalt^{II} chloride in these reactions.

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(Received in UK 30 May 1986)