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A SIMPLE SYNTHESIS OF THIOL ESTERS FROM COPPER-I-MERCAPTIDES AND ACYL CHLORIDES

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Summary: Thiol esters are obtained from acyl chlorides and copper-I-mercaptides in excellent yields.

Thiol esters show higher reactivity and selectivity towards nucleophiles than the corresponding oxygen analoga, which makes them the universal acylation reagents in biochemical processes. New methods for the preparation of thiol esters[1] have been developed in the last few years in order to make profit of these advantages in organic synthesis, particularly for the preparation of macrocyclic natural products[2].

Acyl chlorides were converted to thiol esters by means of thiols in a classical reaction (by adding a base where required); however this transformation gives better yields with thallium[3,4] or tin[5] mercaptides. Looking for an easier synthesis, we found that acyl chlorides (1) with copper-I-mercaptides (2) provide excellent yields of thiol esters (3) after few hours of heterogen reaction (cf table).

(1) (2) (3)

The advantages of the method are the following:

a. Easy availability of copper-I-mercaptides prepared from inexpensive Cu_2O and the corresponding thiols as yellow unsoluble solids (yields: R' = SC_6H_5, 100 %; R' = $SC_6H_4(4)Cl$, 96 %; R' = $SC_6H_4(4)CH_3$, 88 %; R' = $S(t)C_4H_9$, 99 %) [6,7].

b. Copper-I-mercaptides are not water and air sensitive and may be stored without loss of reactivity, at least for months. They are also odourless and unlikely to be toxic.

c. The reaction (1)+(2) → (3) is most easy (stirring of the components in a ratio of 1 : 1.1 eq in an inert solvent, usually diethylether, at room temperature), separation of the thiol esters (3) is very convenient as the insoluble CuCl can be removed by filtration.

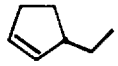
d. The thiol esters (3) obtained after distillation in a kugelrohr oven or after recrystallisation are of high purity; diphenyldisulfide, which is frequently found as a by-product in syntheses of (3) (cf[4]) could not be detected by G.L.C.

As shown by the results of the table, aryl mercaptides display greater reactivity than the t-butyl derivate (cf entries 2 to 5 and 12 to 13). On the other hand, the great difference in reactivity between aliphatic and aromatic carboxylic acid chlorides might provide a possibility of selective activation. Good yields of benzoe acid thiophenol ester were only obtained at higher temperature (boiling toluene) or in the more polar acetonitril as solvent (cf entries 16 to 18). Croton acid chloride reacts smoothly and in very good yield to the corresponding thiol ester (entry 15); using the thiol itself, this transformation gives only moderate yields[8]. Although not extensively explored, the reaction seems to be compatible with several functional groups (cf entries 6, 12, 13, and 14).

In summary, the thiol ester synthesis described above may be a valuable alternative in all processes where direct transformation of a carboxylic acid to the corresponding thiol ester is not required[9].

Table: Preparation of thiol esters

$$R\text{-}CO\text{-}Cl + Cu\text{-}SR' \xrightarrow[20^{o}C]{\text{Ether}} R\text{-}CO\text{-}SR' + CuCl$$

Entry	R	R'	Time (h)	Yield[a] (%)	bp ^{o}C[b]/mm (mp ^{o}C)
1	CH_3	C_6H_5	2	94	50/0.05
2	C_2H_5	C_6H_5	3	99	60-70/0.01
3	C_2H_5	$C_6H_4(4)CH_3$	4	93	90/0.01
4	C_2H_5	$C_6H_4(4)Cl$	3	94	90-100/0.05
5	C_2H_5	$t\text{-}C_4H_9$	17	54[c]	50/20
6		C_6H_5	4	90	80-90/0.01
7	$c\text{-}C_3H_5$	C_6H_5	3	90	(25.5-27.5)
8	$CH(CH_3)_2$	C_6H_5	2	92	90-100/0.01
9	$c\text{-}C_6H_{11}$	C_6H_5	1	85	(33-34)
10	$t\text{-}C_4H_9$	C_6H_5	70	76	80/0.01
11	$t\text{-}C_4H_9$[d]	C_6H_5	3	96	
12	$CH_3OCH_2CH_2$	C_6H_5	2	85	150/0.4
13	$CH_3OCH_2CH_2$	$t\text{-}C_4H_9$	0.5[e]	78	110-120/20
14	$ClCH_2$	C_6H_5	70	79	(41-43)
15	$CH_3CH{=}CH$	C_6H_5	2	86	80-90/0.3
16	C_6H_5	C_6H_5	150	16	130-140^{o}C/0.01
17	C_6H_5	C_6H_5	9[f]	70	(56-57)
18	C_6H_5	C_6H_5	24[g]	98	
19	$C_6H_5SCOCH_2CH_2COSC_6H_5$[h]		55	91	(87.5-89)

For footnotes see next page.

Footnotes to table:

[a] Isolated yield; ^{1}H-NMR and IR spektra are in accordance with the proposed structure. [b] Air bath temperature. [c] The volatility of the product may have diminished the yield. [d] Pivalyl bromide was used. [e] In boiling acetonitril. [f] In boiling toluene. [g] Acetonitrile, 20°C. [h] Starting material: succinyl chloride

References and Notes

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