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A FACILE SYNTHESIS OF CARBOXYLIC THIOL ESTERS FROM CARBOXYLIC ACIDS AND THIOLS

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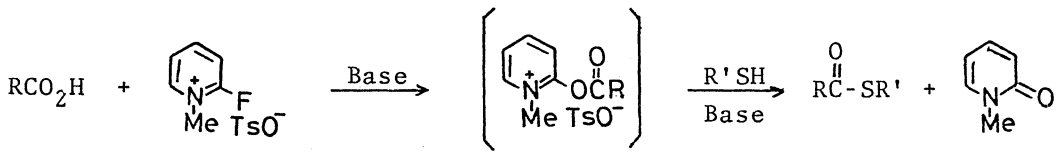
Various thiol esters are prepared in good yields by the reaction of thiols with acyloxypyridinium salts formed in situ from free carboxylic acids and 2-fluoro-1-methylpyridinium p-toluenesulfonate.

Recently, 2-halopyridinium salts (halogen=F,Cl,Br) are found to be effective coupling reagents for the preparation of various carboxylic acid derivatives starting from equimolar amounts of free carboxylic acids and nucleophiles such as alcohol,[1] amine,[2] fluoride,[3] or cyclic imidate.[4] The present paper describes a convenient method for the preparation of carboxylic thiol esters from carboxylic acids and thiols via acyloxypyridinium salts 2, formed by the reaction of carboxylic acids with 2-fluoro-1-methylpyridinium p-toluenesulfonate (1) in the presence of triethylamine (or tri-n-butylamine).

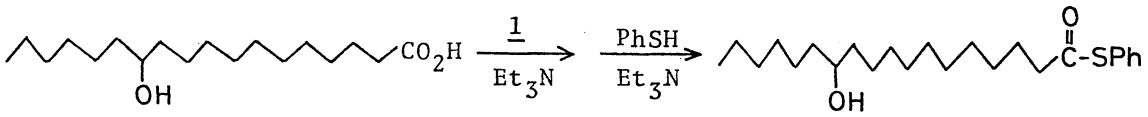


1 2

The following is a general procedure for preparing thiol esters by the present method. To a stirred suspension of 2-fluoro-1-methylpyridinium p-toluenesulfonate (1.06 mmol) in dichloromethane (1 ml) cooled to -15 ∿ -10°C in an ice-salt bath was slowly added a mixture of a carboxylic acid and triethylamine (1 mmol each) in dichloromethane (2 ml) under an argon atmosphere. The resulting solution was stirred for a certain period at the same temperature and then treated with a thiol and triethylamine (1 mmol each) in dichloromethane (2 ml). The mixture was stirred under conditions indicated in the Table and dichloromethane was evaporated under reduced pressure to give an oily residue, from which the corresponding thiol ester was obtained either directly by preparative tlc or after conventional work-up with ease. It is noted that when alkanethiols and α-pyridinethiol are employed as thiols, stirring of carboxylic acids and 1 for 20 ∿ 30 min is advantageous because the formation of relatively inert acyl fluoride[3] can be avoided.

Furthermore, preparation of the thiol ester derived from a hydroxy acid (12-hydroxyoctadecanoic acid) and benzenethiol was successfully accomplished without protecting the hydroxyl group when 1 was added to the carboxylic acid and

triethylamine at room temperature, and the resulting mixture was treated with benzenethiol and triethylamine.



Concerning the direct preparation of thiol esters from free carboxylic acids, a method utilizing triphenylphosphine and diphenyl disulfide[5] (or 2,2'-dipyridyl disulfide[6]) was reported from our laboratory, and recently Yamada et al.[7] reported a method using diethyl phosphorocyanidate or diphenylphosphorazidate.

The present reaction provides a convenient method for the preparation of thiol esters in respects of (1) direct synthesis of thiol esters from equimolar amounts of free carboxylic acid and thiol, and (2) mildness of reaction conditions.

Table Synthesis of Thiol Esters

Acid R	Thiol R'	Conditions[a] Step 1 Temp.	Step 1 Time(min)	Step 2 Temp.	Step 2 Time(min)	Yield (%) of Thiol Ester
C_6H_5	C_6H_5	A	60	A	120	87
$C_6H_5CH_2$	C_6H_5	A	60	A	120	96
$C_6H_5(CH_2)_2$	C_6H_5	A	60	A	120	84[b]
$(CH_3)_3C$	C_6H_5	A	60	A	120	88
$CH_3CO(CH_2)_2$	C_6H_5	A	60	A	120	83
$HO_2C(CH_2)_4$	C_6H_5[c]	A	60	A	120	79[d]
$C_6H_5CH_2$	n-C_4H_9	A	60	A	120	81[b]
$C_6H_5CH_2$	s-C_4H_9	A	60	refl.	120	81
$C_6H_5CH_2$	t-C_4H_9	A	20	r.t.	B	84
$C_6H_5CH_2$	α-C_5H_5N[e]	A	30	r.t.	B	79
	C_6H_5	A	15	A	35	84
$CH_3(CH_2)_5CH(CH_2)_{10}$ OH	C_6H_5	r.t.	30	r.t.	60	75

a) A = temperature of an ice-salt bath (-15 ∿ -5°C), B = overnight.
b) Tri-n-butylamine was used as a base.
c) Two equimolar amounts of benzenethiol were used.
d) The yield of hexanebis(S-phenyl thioate).
e) α-Pyridinethiol.

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