Tetrahedron Letters No. 31, pp 2875 - 2878.
0040-4039/79/0729-2875$02.00/0

A NEW METHOD FOR THE SYNTHESIS OF 2-PYRIDINETHIOL CARBOXYLIC ESTERS

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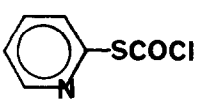
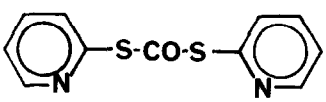
Summary: An effective and convenient synthesis of 2-pyridinethiol esters of carboxylic esters has been developed which involves the interaction of a carboxylate salt with the S-chloroformyl derivative of 2-pyridinethiol.

2-Pyridinethiol esters of carboxylic acids have assumed an increasingly important role in synthesis, primarily because of their new-found utility as acylating agents in the formation of macrocyclic lactones,[1,2] peptides,[3] and ketones.[4] Although several methods are available for the synthesis of 2-pyridinethiol esters, each suffers from operational problems and limits with regard to scope. The most frequently used and most nearly general process, due to Mukaiyama,[3a] involves the interaction of a carboxylic acid, triphenylphosphine and 2,2'-dipyridyldisulfide. A major difficulty associated with this method is the necessity for chromatographic separation of the co-products 2-pyridinethiol, triphenylphosphine oxide, and any excess of the disulfide and phosphine reagents, which is difficult to carry out on a larger than decimolar scale and leads to considerable loss of product by reaction on the adsorbant (usually silica gel). The other known procedures are even less satisfactory, for example, that using dicyclohexylcarbodiimide for carboxyl activation,[3c,5] or the coupling of thallous 2-pyridinethiolate with an acid chloride.[6]

We wish to report the use of a new reagent, 2-thiopyridyl chloroformate (I), for conversion of acids to 2-pyridinethiol esters under extremely mild conditions. The chlorothioformate I, conveniently prepared from phosgene and 2-pyridinethiol in 96% yield, can be handled in air and is stable for up to one month if stored at -25° C. The reagent is unstable to water and silica gel, and decomposes to the bisthioformate II.



I

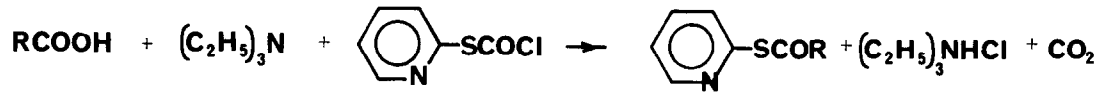


II

Reaction of equimolar amounts of I, an acid, and triethylamine at 0° C for 0.5 hr affords the 2-pyridinethiol ester in essentially quantitative yield (see Table).

Pure esters of 2-pyridinethiol are easily obtained since carbon dioxide is liberated and triethylammonium chloride is easily removed by filtration (Procedure A) or by washing with dilute acid if an aqueous workup is used (Procedure B). The effectiveness of the reaction conditions is dramatically illustrated by the successful synthesis of 5, which could not be prepared by any of the existing methods.[3a,3c,5,6]

Representative procedures are given below.



Preparation of 2-Thiopyridyl Chloroformate. Phosgene (10-15 mmols) is dissolved in a mixture of toluene (5 ml) and methylene chloride (5 ml) at 0°C. A solution of triethylamine (2.15 mmol, 0.30 ml) and 2-pyridinethiol (2.0 mmol, 222 mg) in methylene chloride (10 ml) is added dropwise over five minutes. The resultant colorless, homogeneous solution is stirred for ten minutes, and excess phosgene and methylene chloride are removed in vacuo. Hexane (20 ml) is added and the precipitated triethylamine hydrochloride is removed by filtration. The flask is rinsed with an additional volume of toluene (5 ml) and hexane (20 ml) and the solution is filtered. The combined filtrates are concentrated in vacuo to afford 330 mg (96%) of the reagent as a colorless oil. The reagent is dissolved in methylene chloride (10 ml), and if protected from moisture, can be stored at -25°C for several weeks with no apparent decomposition; infrared max (CH_2Cl_2), 1765 $cm.^{-1}$ (C=O); pmr ($CDCl_3$), 8.64 m(1H), 7.75 m(2H), 7.38 m(1H); mass spectrum, (m/e, int) 175 (M+2, 8), 173 (M, 25), 138 (53), 78 (100). The reagent can be handled in air, but must be protected from water, since it is transformed readily into bis-thiopyridyl carbonate (II), infrared max (CH_2Cl_2) 1715 $cm.^{-1}$

General Procedures for Formation of 2-Pyridinethiol Esters from I.

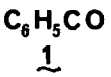
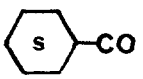
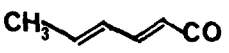
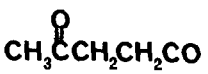
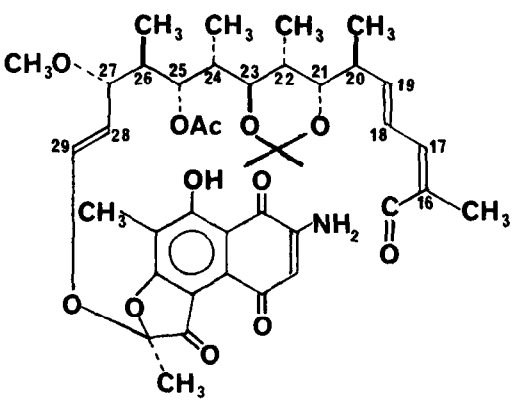
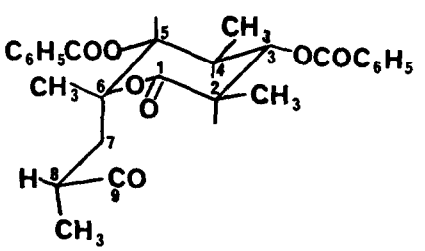
A. The acid (1.0 mmol) and triethylamine (1.1 mmol, 0.15 ml) are dissolved in ether (10 ml) at 0°C. The reagent I (1.0 mmol) in methylene chloride is added, and the contents are stirred for 0.5 hr. The solution is diluted with ether (25 ml), some $MgSO_4$ added, and the mixture is filtered to remove the precipitated triethylamine hydrochloride and $MgSO_4$. Removal of the ether in vacuo affords the thiopyridyl ester in high yield, the only contaminant being 1-2% of the thiocarbonate II.

B. The acid (1.0 mmol) and triethylamine (1.10 mmol, 0.15 ml) are dissolved in methylene chloride (5 ml) at 0°C. The reagent I (1.0 mmol) in methylene chloride is added, and the contents are stirred for 0.5 hr. The solution is diluted with methylene chloride (25 ml) and washed with cold 10% $NaHCO_3$ (10 ml), cold 5% HCl (10 ml) and finally saturated NaCl (10 ml). After drying ($MgSO_4$) and removal of solvent in vacuo, the thiolpyridine ester is obtained.

Products obtained from either procedure A or B are sufficiently pure for most synthetic applications after more rigorous drying, which is readily accomplished by addition of toluene and concentration under reduced pressure three times.[8]

TABLE I

Preparation of 2-Pyridinethiol Esters, RCOS- 

RCO in Product	% Yield	
	Procedure A	Procedure B
 1	98	100
 2	100	100
 3	95	97
 4	98	95
 5	—	95
 6	—	97[7]

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8. This research was financially assisted by a grant from the National Institute of Health.

(Received in USA 12 April 1979)