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LEWIS ACID-PROMOTED REACTION OF 2-ALKOXY-3,5-DINITROPYRIDINES WITH THIOLS. A NEW METHOD FOR THE SYNTHESIS OF UNSYMMETRICAL SULFIDES

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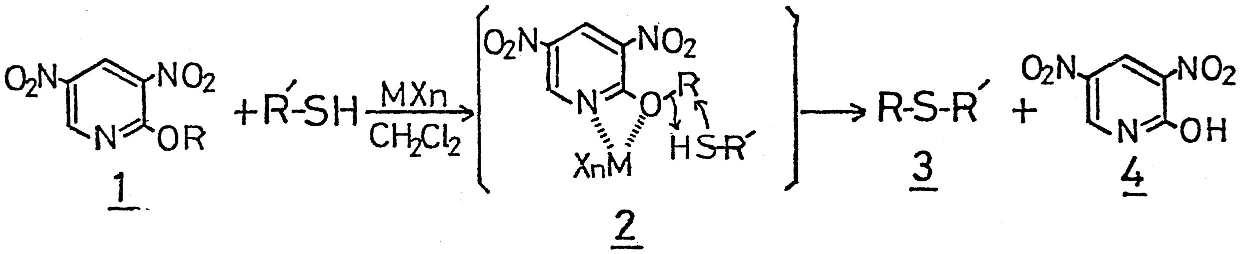
2-Alkoxy-3,5-dinitropyridines, easily prepared from 2-fluoro-3,5-dinitropyridine and alcohols react with various thiols in the presence of Lewis acids to give the corresponding unsymmetrical sulfides in good yields.

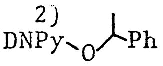
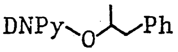
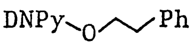
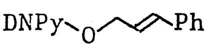
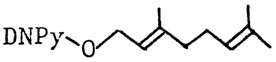
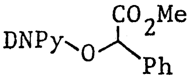
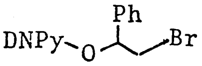
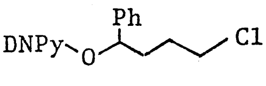
As a part of our continuing investigation on the exploration of new synthetic reactions by use of 2-halopyridinium salts, we wish to report here a new method for the preparation of unsymmetrical sulfides by the Lewis acid-promoted reaction of 2-alkoxy-3,5-dinitropyridines 1 with thiols.



Concerning the synthesis of unsymmetrical sulfides, most of the literature methods involve the reactions of thiols with alkyl halides,[1)] alkyl sulfates,[2)] and alkyl sulfonates,[3)] respectively, by use of sodium hydroxide or other strong bases. On the other hand, it has been recently established in our laboratory that 2-alkoxy-1-alkylpyridinium salts, prepared in situ from 1-alkyl-2-halopyridinium salts and alcohols,reacted with thiols in the presence of tertiary amine to give the corresponding sulfides in good yields.[4)]

In the present experiment, the reaction of 2-alkoxy-3,5-dinitropyridines with thiols was carried out in the presence of Lewis acids with the consideration that

Table I. The Preparation of Sulfides[1]

1	Thiol	MXn	Temp.(°C)	Time(hr)	Yield(%)
a) [2] 	$PhCH_2SH$	cat.$BF_3.OEt_2$	-78	4	78
	Ph-SH	cat.$BF_3.OEt_2$	-78	4	88
	t-BuSH	cat.$BF_3.OEt_2$	-78	6	76
b) 	$PhCH_2SH$	$TiCl_4$[3]	r.t.	4	90
	Ph-SH	$TiCl_4$	r.t.	4	93
	t-BuSH	$TiCl_4$	r.t.	4	94
C) 	$PhCH_2SH$	$TiCl_4$	r.t.	overnight	62
	Ph-SH	$TiCl_4$	r.t.	overnight	61
	t-BuSH	$TiCl_4$	r.t.	overnight	71
d) 	$PhCH_2SH$	cat.$BF_3.OEt_2$	r.t.	2	64
	Ph-SH	cat.$BF_3.OEt_2$	r.t.	6	74
	t-BuSH	cat.$BF_3.OEt_2$	r.t.	4	73
e) 	t-BuSH	$TiCl_4$	r.t.	1	91
	$PhCH_2SH$	$TiCl_4$	-78	1	85
	Ph-SH	$TiCl_4$	-78	1	92
f) 	$PhCH_2SH$	$TiCl_4$	r.t.	overnight	60
g) 	$PhCH_2SH$	$TiCl_4$	-78	3	85
h) 	$PhCH_2SH$	$TiCl_4$	-78	3	91

1) All compounds exhibited ir and nmr spectral data in accordance with assigned structures.

2) DNPy = 3,5-dinitro-2-pyridyl

3) An equimolar amount of $TiCl_4$ was used. No reaction occurred when an equimolar amount of $BF_3.OEt_2$ was used.

the coordination of Lewis acid to alkoxypyridine would form similar reactive species to those assumed in the case of the pyridinium salt.[4)]

A typical procedure is described for the preparation of benzyl α-methylphenethyl sulfide (3b). A methylene chloride solution (1 ml) of $TiCl_4$ (190 mg, 1 mmol) was added to a stirred solution of 2-(α-methylphenethyl)oxy-3,5-dinitropyridine (1b) (303 mg, 1 mmol) and phenylmethanethiol (124 mg, 1 mmol) in methylene chloride (4 ml) at room temperature under an argon atmosphere. The mixture was stirred for 4 hr at this temperature, and an aqueous K_2CO_3 (0.3 g, ca. 2 mmol) solution (10ml) was added to the mixture. After filtration of the resulting precipitate, usual work-up of the filtrate and purification by column chromatopraphy (silica gel) gave benzyl α-methylphenethyl sulfide (218 mg) in 90% yield. In a similar manner various sulfides were prepared in good yields as summarized in Table I.

Various alkoxypyridines 1 were prepared from 2-fluoro-3,5-dinitropyridine (5) and alcohols in the presence of triethylamine in high yields (Table II).

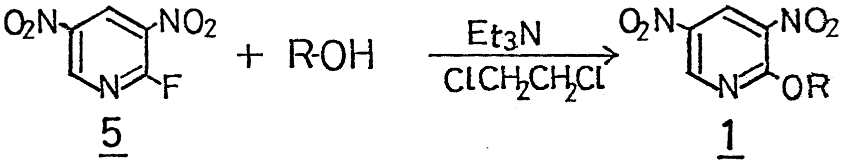
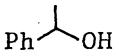
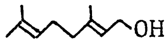
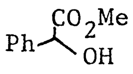
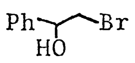
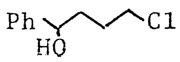


Table II. The Preparation of Alkoxypyridines 1

	ROH	Temp.	Time(hr)	Yield (%)
a)		refl.	3	81
b)		refl.	3	90
c)		refl.	3	91
d)		r.t.	3	79
e)		r.t.	1.5	81
f)		refl.	3	74
g)		r.t.	overnight	77
h)		r.t.	5	74

As shown in Table I, 3,5-dinitro-2-(1-phenylethoxy)pyridine (1a), derived from a benzylic alcohol, reacted with phenylmethanethiol at -78°C in the presence of a catalytic amount of $BF_3.OEt_2$ to give the corresponding benzyl 1-phenylethyl sulfide in 78% yield. On the other hand, 2-(α-methylphenethyl)oxy-3,5-dinitropyridine (1b), derived from a non-benzylic alcohol, reacted with thiols very slowly even in the presence of an equimolar amount of $BF_3.OEt_2$ at room temperature. After screening Lewis acids such as $TiCl_4$, $AlCl_3$, $ZnCl_2$, etc., instead of $BF_3.OEt_2$, it was found that 1b reacted smoothly in the presence of an equimolar amount of $TiCl_4$ at room temperature to give the corresponding sulfides in good yields.

Contrary to the 3,5-dinitropyridyl ethers, no desired sulfide was obtained by the reaction of 2,4-dinitrophenyl ether, p-toluenesulfonate, or methanesulfonate with thiols.

It is noted that the present method is successfully applied to the preparation of various unsymmetrical sulfides starting from alcohols in two steps. Even in the case of haloalcohols, halosulfides (3 g, 3 h), which cannot be obtained by the conventional methods under basic conditions, was produced exclusively.

Further works on the utility of 2-substituted-3,5-dinitropyridine derivatives are now in progress.

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