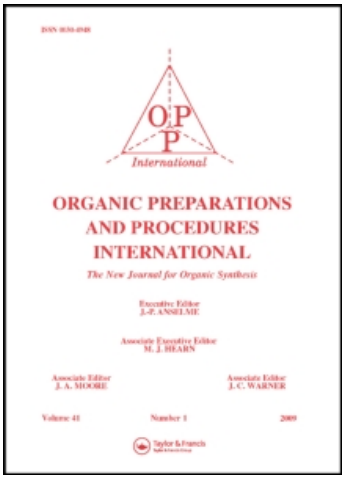

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4-PIPERIDINOPYRIDINE AS AN EFFECTIVE CATALYST FOR THIONE-THIOL REARRANGEMENT OF XANTHATES

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4-PIPERIDINOPYRIDINE AS AN EFFECTIVE CATALYST FOR THIONE-THIOL REARRANGEMENT OF XANTHATES

Submitted by (11/08/91)

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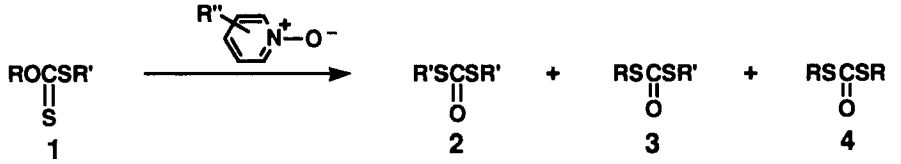
A short synthesis of thiols from alcohol under neutral non-aqueous conditions would be very attractive to synthetic chemists.[1] Thus, combination of the catalytic thione-thiol rearrangement of *O,S*-dialkyl dithiocarbonates (xanthates, **1**) and aminolysis of the rearranged products with ethanolamine serves as an efficient method for the generation of thiols,[2] in which all of the reactions and work-up can be carried out in a single distilling flask. In this context, we reported that pyridine *N*-oxides bearing electron-donating substituents are useful catalysts for the rearrangement of *O,S*-dialkyl xanthates (**1**) to *S,S*-dialkyl dithiocarbonates (**2, 3, 4**).[3]



a) R = Et, R' = Me **b**) R = *n*-Pr, R' = Me **c**) R = *n*-Bu, R' = Me **d**) R = *i*-Pr, R' = Me

Based on these results,[3] we considered that the parent pyridines bearing electron-donating groups might also show similar catalytic activity because they have a high-lying highest occupied molecular orbital (HOMO) with the large HOMO coefficient and a negative net charge on the pyri-

dine nitrogen atom. We now report the catalytic effect of 4-dialkylamino- pyridines on the thione-thiol rearrangement of xanthates.

We first compared the relative reactivity of several pyridines by using *O*-ethyl *S*-methyl xanthate (**1a**, R = Et) as a substrate. The reaction was carried out by warming a mixture of the xanthate and various amounts of amines at 80-100°. The product mixtures were analyzed by nmr.

TABLE 1. Effect of Reactant/Catalyst Ratio on the Yield of **2a**, **3a** and **4a** in the Reaction of *O*-Ethyl *S*-Methyl Xanthate (**1a**)

Exp. No.	Pyridines Cat:**1**	Temp (°C)	Time (hrs)	Total Yield of the Products (%)
4-Dimethylamino (DMAP)[a]				
1	0.1:1	80	4.0	56
4-Piperidino (PP)[b]				
2	0.5:1	80	1.5	64
3	0.2:1	80	2.0	61
4	0.1:1	80	3.0	64[c]
5	0.05:1	80	6.0	72
6	0.02:1	80	10.0	72
3,5-Dimethyl[b]				
7	0.5:1	100	3.0	74
4-Methyl[b]				
8	0.5:1	100	4.0	67
Pyridine[b]				
9	0.5:1	100	24.0	40

a) In DMSO-D_6. Use of DMAPNO gave the dithiol esters in 87% yield. b) No solvent was used. c) Use of 4-Piperidinopyridine *N*-oxide (PPNO) gave the dithiol esters in 75% yield.

Table 1 shows that a small amount of 4-dimethylaminopyridine (DMAP) showed sufficient activity to induce the rearrangement, whereas a large amount of 3,5-dimethylpyridine (3,5-lutidine) was required for the same effect. The activity of DMAP is assumed to be comparable to that of the corresponding *N*-oxide (DMAPNO).[3b] In the cases of DMAP and DMAPNO, dimethyl sulfoxide (DMSO) was used as solvent because of the low solubility in xanthates. In contrast, 4-piperidinopyridine (PP) which is freely miscible with xanthates, showed high catalytic activity. The yield is not sensitive to reactant/catalyst ratio and good yields were obtained at a reactant to catalyst molar ratio of 20-50 (Exp. No. 5, 6). When a large amount of catalyst was used (Exp. No. 2), the yield of the dithiocarbonates decreased, presumably a consequence of formation of the pyridinium salt and its decomposition product (ethyl methyl sulfide).

The application of PP as catalyst to several xanthates is shown in Table 2. Primary *O*-alkyl xanthates easily underwent the thione-thiol rearrangement to give mixtures of the dithiol esters in moderate yields. On the other hand, secondary xanthates required more forcing reaction conditions.

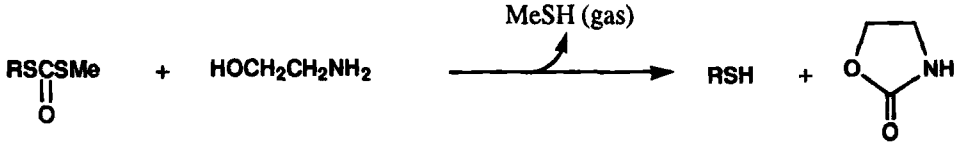
TABLE 2. Catalytic Rearrangement of Xanthates by Piperidinopyridine (PP)

1		Reaction Conditions[a]		Yield(%)			
R	R'	Temp. (°C)	Time (hrs)	2	3	4	Total
Et	Me	80	3.0	17	31	17	65
n-Pr[b]	Me	80	7.0	20	34	17	71
		90	3.0	25	45	18	88
n-Bu[b]	Me	80	8.0	21	36	18	75
		90	4.0	20	38	17	75
i-Pr[b]	Me	110	4.0	18	30	8	56
		130	1.5	18	29	9	56
$C_6H_5CH_2CH_2$	Et	90	4.0	16	32	17	65[c]
$C_5H_4NCH_2CH_2$[d]	Et	100	6.0	18	37	10	65[c]
Cyclohexyl[b]	Me	130	35.0	1	12	0	13[e]
		150	11.0	1	4	2	7[e]

a) PP/I=0.1, no solvent was used. b) Use of PPNO for **1b**, **1c**, **1d** and **1e** gave the productss in 74, 68, 53 and 10 % yields, respectively. c) Isolated yield. d) 2-(2-Pyridyl)ethyl moiety. e) Cyclohexene was produced *via* Chugaev reaction.

The order of reactivity of xanthates (Et > *n*-Pr ~ *n*-Bu > iso-Pr > cyclohexyl) is consistent with that found in the case of DMAPNO.[3a] In the case of *O*-cyclohexyl *S*-methyl xanthate, the yield was lower than that observed in the case of DMAPNO.[3a] This may be due to steric interference between the substrate and catalyst. The reaction obeyed pseudo first-order kinetics and the apparent rate constant was proportional to the concentration of amines used.[4] These facts suggest that the reaction proceeds *via* S_N2-type nucleophilic attack of the nitrogen atom of DMAP on the *O*-alkyl group of xanthates.

Yoshida[5] reported that *O*,*S*-dimethyl xanthate reacted with triethylamine to give the quaternary salt,[6] during which the thione-thiol rearrangement occurred. However, the reaction with triethylamine is limited only to *O*-methyl and *O*-ethyl *S*-alkyl xanthates. The present method can be generally applied to the xanthates of primary alcohols.



The rearranged products are aminolyzed with 2-aminoethanol to give thiols.[2]

EXPERIMENTAL SECTION

IR spectra were determined on a Hitachi 270-30 infrared spectrometer equipped with a grating. ^1H NMR spectra were obtained on a JEOL GX-400 spectrometer for *ca.* 10% (w/v) solutions in $CDCl_3$.

Catalytic Rearrangement of *O,S*-Dialkyl Xanthates to *S,S*-Dialkyl Dithiocarbonates (General Procedure).- A solution of *O,S*-dialkyl xanthate (**1**) and 0.1 molar eq of 4-piperidino- pyridine was heated at 80° until the spot for **1** was no longer visible by thin-layer chromatography (TLC) on silica gel. After cooling, the products were purified by choromatography on silica gel or by distillation under reduced pressure. The products derived from *O*-ethyl, *O*-propyl, *O*-isopropyl, *O*-butyl and *O*-cyclohexyl *S*-methyl xanthates were identified by comparison of the spectral data with those of the authentic samples.[3,5,7]

The physical data of the newly prepared samples are as follows.

***S*-[2-(2-Pyridyl)ethyl] *S*-Ethyl Dithiocarbonate.**- This compound was isolated as a colorless oil. ^{1}H NMR: δ 1.29 (t, 3H, J = 7.3 Hz, CH_2CH_3), 2.99 (q, 2H J = 7.3 Hz, CH_2CH_3), 3.11 (t, 2H, J = 6.8 Hz, $ArCH_2$), 3.41 (t, 2H, J = 6.8 Hz, $ArCH_2CH_2$), 7.13 (m, 1H, C_5-H), 7.22 (m, 1H, C_3-H), 7.60 (m, 1H, C_4-H), 8.53 (m, 1H, C_6-H); EI-ms: *m/z*: 226, (M^+), 138 ($ArCH_2CH_2S$-); IR (film): 2932 (aromatic), 1644 (C=O), 868 (C-S) cm^{-1}.

Anal. Calcd for $C_{10}H_{13}NOS_2$: C, 52.86; H, 5.77; N, 6.17. Found: C, 52.74; H, 5.71; N, 6.20.

***S,S*-Di[2-(2-pyridyl)ethyl] Dithiocarbonate.**- This compound was isolated as a colorless oil. ^{1}H NMR: δ 3.12 (t, 2H, J = 7.3 Hz, $ArCH_2$), 3.41 (t, 2H, J = 7.3 Hz, $ArCH_2CH_2$), 7.13 (m, 1H, C_5-H), 7.16 (m, 1H, C_3-H), 7.61 (m, 1H, C_4-H), 8.54 (m, 1H, C_6-H); EI-ms: *m/z*: 304 (M^+) 138 ($ArCH_2CH_2S$-); IR (film): 2936 (aromatic), 1644 (C=O), 868 (C-S) cm^{-1}.

Anal. Calcd for $C_{15}H_{16}N_2OS_2$: C, 59.20; H, 5.30; N, 9.21. Found: C, 59.20; H, 5.06; N, 9.42.

***S*-(2-Phenylethyl) *S*-Ethyl Dithiocarbonate.**- This compound was isolated as a colorless oil. ^{1}H NMR: δ 1.29 (t, 3H, J = 7.3 Hz, CH_3), 2.75-2.78 (m, J = 7.3 Hz, CH_2CH_3), 2.99 (q, 2H, J = 7.3 Hz, $PhCH_2CH_2$), 3.20 (q, 2H, J = 7.3 Hz, $PhCH_2$), 7.17-7.31 (m, 5H, aromatic H); EI-ms: *m/z*: 227 (M^+), 105 ($PhCH_2CH_2$-), 91 ($PhCH_2$); IR (film): 2928 (aromatic), 1644 (C=O), 870 (C-S) cm^{-1}

Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.40; H, 6.24. Found: C, 58.22; H, 6.36.

***S,S*-Di(2-phenylethyl) Dithiocarbonate.**- This compound was isolated as a colorless oil. ^{1}H NMR: δ 2.87 (t, 2H, J = 7.3 Hz, SCH_2), 3.19 (q, 2H, J = 7.3 Hz, $PhCH_2$), 7.15-7.30 (m, 5H, aromatic H); EI-ms: *m/z*: 302 (M^+), 242 (M^+-COS), 151 (M^+-COS-$PhCH_2$), 104 ($PhCH_2CH_2$); IR (film): 2956 (aromatic), 1644 (C=O), 872 (C-S) cm^{-1}.

Anal. Calcd for $C_{17}H_{18}OS_2$: C, 67.54; H, 6.00. Found: C, 67.63; H, 5.94.

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4) The activation enthalpy and entropy for the reaction of *O*-ethyl *S*-methyl xanthate with PP in DMSO are 24.7 kcal/mol and -11 e.u. respectively. In the reaction, a coloration due to a charge transfer complex[3b] was not observed in contrast to the case of pyridine *N*-oxides.

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6) Reaction of *O,S*-dimethyl xanthate with triethylenediamine gave the stable quaternary salt. The reaction with PP may proceed through the formation of a similar quaternary salt which may easily dissociate by heating.

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A NOVEL SYNTHESIS OF 2,3-DIHYDRO[1,5]BENZOTHIAZEPIN-4(5H)-ONES

Submitted by (12/26/91) Jean-Charles Lancelot[†], Bertrand Letois[†], Carmela Saturnino[†], Paolo De Caprariis[††] and Max Robba[*†]

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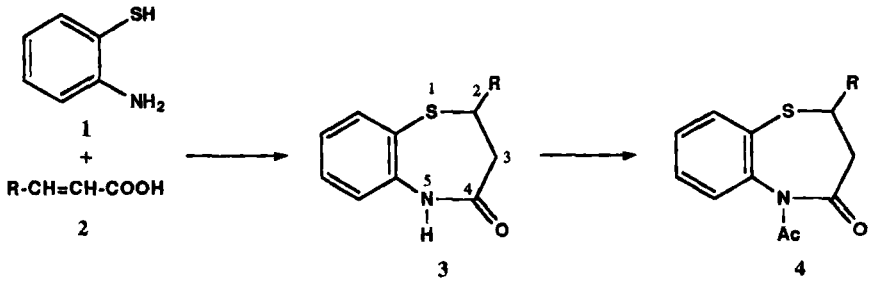
Benzothiazepines such as *Diltiazem*[1] or *Thiazesim*[2] are currently used as antidepressant, coronary vasodilator and antiangina agents. The present paper describes the preparation of new 2,3-dihydro[1,5]benzothiazepines diversely substituted at the 2-position.



a) R = 3-pyridyl
b) R = *p*-$NO_2C_6H_4$
c) R = *p*-FC_6H_4
d) R = 2-furyl
e) R = 2-thienyl
i) R = 5-methyl-2-thienyl
g) R = 5-bromo-2-thienyl
h) R = 3-thienyl
i) R = *n*-butyl