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Reduction of Activated Thiopyridyl Compounds by Zinc Metal

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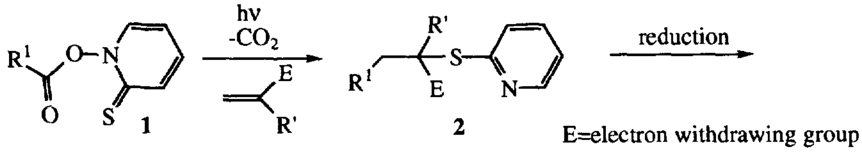
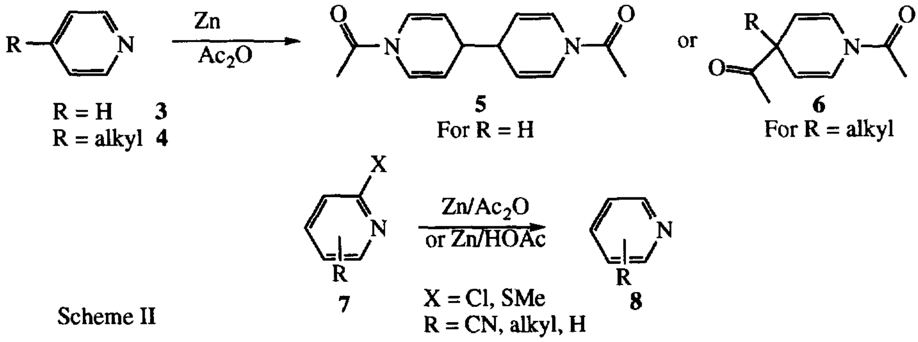
Abstract: Starting from thiopyridyl compounds bearing a radical stabilizing group in α-position to the thiopyridyl moiety, the thiopyridyl group can be easily removed upon reduction by zinc metal in acetic acid.

In the course of our work regarding the further transformation of adducts **2** obtained by the Barton-decarboxylation method[2] employing thiohydroxamic acid esters **1** we got interested in the behaviour of these compounds, bearing a thiopyridyl moiety in α-position to a radical stabilizing group in the presence of a reducing metal such as zinc (Scheme I).



Scheme I

For the reduction of pyridines by zinc metal three main different reaction pathways, depending on the substitution pattern of the pyridine nucleus, are known in the literature (Scheme II).



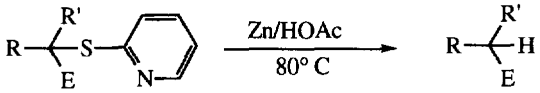
Scheme II

Unsubstituted pyridine (**3**) itself affords upon treatment with zinc in acetic anhydride the diacetylated dimeric dihydropyridine **5**, while 4-alkylsubstituted pyridines **4** yield the 1,4-diacylated dihydropyridines **6**.[3,4]

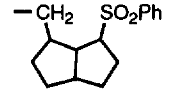
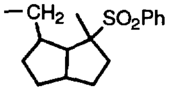
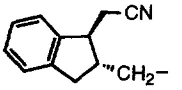
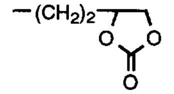
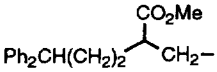
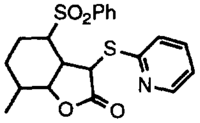
Pyridines like **7** bearing a chlorine or a methylthiofunction in α-position undergo, upon treatment by zinc in acetic acid or in acetic anhydride, hydrodehalogenation and hydrodesulfination respectively yielding the corresponding 2-unsubstituted pyridines **8** without further reduction of the pyridine nucleus.[5,6] On the contrary, pyridines bearing a large variety of substituents (alkyl, carboxyl, ester, amide, amine) in 2-position are reported to be inert under these reaction conditions and are recovered unchanged.[4,5]

We found that treatment of compounds **2**, prepared according to reported procedures,[2] with commercial zinc-powder in acetic acid at 80° C[7] led to a clean fission of the alkyl-thio bond thus yielding the corresponding desulfurized alkyl derivatives **9** (Table I).

Table I



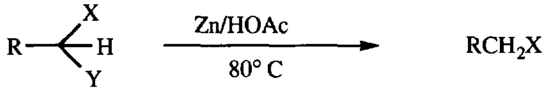
2 **9**

2	R	R'	E	**9**	yield[%]
a	-CH2CHPh2	H	H	**a**	-
b	-(CH2)2CHPh2	H	SO2Ph	**b**	96
c	-(CH2)15CH3	H	SO2Ph	**c**	98
d		H	SO2Ph	**d**	97
e		Me	SO2Ph	**e**	quant.
f		H	SO2Ph	**f**	97
g		H	SO2Ph	**g**	72
h	-(CH2)2CHPh2	H	CO2Me	**h**	95
i	 $\mathrm{Ph_2CH(CH_2)_2CH(CO_2Me)CH_2{-}}$	H	CO2Me	**i**	87
j				**j**	98
k	-(CH2)2CHPh2	H	CN	**k**	33

Compounds **2** bearing a radical stabilizing group in α-position to the thiopyridyl moiety were transformed smoothly in 3 hours; in the case of the quaternary substituted derivative **2e** the reaction was complete after 15 min only. As can be seen from table I, sulfone, nitrile, ester, lactone and carbonate functionalities present in the molecule are tolerated except for **2k**, bearing the nitrile function at the reaction center. In this case the starting material is sensitive against hot acetic acid. A blank experiment showed that **2k** decomposed completely during 1 hour at 80° C in acetic acid even in the absence of zinc.

Since the unfunctionalized thiopyridyl compound **2a** did not react at all under these conditions (7 hours, 80°C), we thought that the thiopyridyl group might not be involved in the first steps of the reduction and that it could only be the donor-acceptor substitution which facilitates the reduction. Thus a variety of compounds **10** similar to **2** have been tested under the same reaction conditions (Table II).

Table II



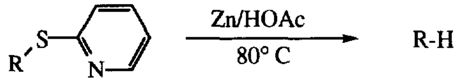
10 **11**

10	R	X	Y	**11**	yield
a	$-(CH_2)_3Ph$	SO_2Ph	SPh	**a**	-
b	$-(CH_2)_3Ph$	SO_2Ph	SO_2Ph	**b**	-
c	H	SPh	SPh	**c**	-
d	$-CH=CH_2$	H	SO_2Ph	**d**	-

In all cases compounds **10** were recovered unchanged after treatment with zinc powder in acetic acid at 80° C for several hours, thus demonstrating that the thiopyridyl group is essential for the reduction of compounds **2**. The inertness of compounds **10** indicates that functionalities such as aldehydes or ketones protected as thioketals can be present in compounds like **2** without interfering in the course of the reduction.

Since we expect the reduction to proceed *via* a radical mechanism, compounds **12** bearing tertiary or benzylic groups in α-position to the thiopyridyl function have also been investigated (Table III).

Table III

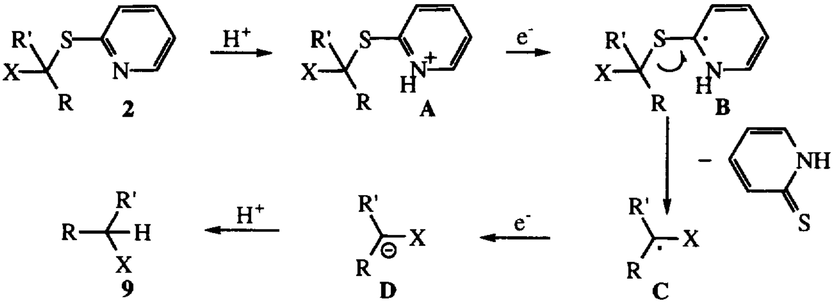


12 **13**

12	R	products	yield[%] of **13**
a	1-adamantyl	no reaction	-
b	CH_2Ph	**13b**	volatile product
c	$CHPh_2$	**13c** + R-R	75
d	CPh_3	**13d** + R-OH	50

While the adamantyl substituted **12a** did not react under the reaction conditions, indicating that the radical stabilizing effect of a tertiary alkyl group is not sufficient to afford the reduction, phenyl substituents render the molecule sufficiently labile to reduction so that the desulfurized compounds **13** were obtained. The pyridylthioether **12d** is quite susceptible to acid hydrolysis and a large amount of triphenylmethanol was obtained.

Although trapping experiments employing **2b** and allylacetate or **11b** and phenylvinylsulfone were not successful, in analogy to the formation of compounds **1** and **2**[3,4] the course of the reaction can be rationalized assuming a radical mechanism (Scheme III).



Scheme III

In a preliminary step, compounds **2** would be protonated to yield the pyridinium salt **A** which then could be reduced to the radical **B**. Heterolytic rupture of the alkyl-thio bond of radical **B** would lead to the stabilized radical **C** which could then be further reduced to the stabilized carbanion **D**. This reduction step should probably proceed very quickly, thus explaining the failure of the trapping experiments. Protonation of **D** would then yield the desulfurized compounds **9**.

The substitution of the thiopyridyl group of compounds like **2** by hydrogen has up to now been realized employing nickel boride or sodium telluride.[2a] While the method presented here is superior in yields to the nickel boride reduction, it offers a suitable alternative for the sodium telluride methodology, employing cheap and untoxic products and a very simple procedure affording comparable yields of compounds **9**.

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References and Notes

1 Present address: Laboratoire de Recherches Organiques associé au C.N.R.S., ESPCI, 10 rue Vauquelin, 75231 Paris, Cedex 5, France

2 (a) Barton, D. H. R.; Boivin, J.; Crépon, E.; Sarma, J; Togo, H.; Zard, S. Z. *Tetrahedron*, **1991**, *34*, 7091-7108. (b) Boivin, J.; Crépon, E.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 199-202. (c) Barton, D. H. R.; da Silva, E.; Zard, S. Z. *J. Chem. Soc. Chem. Commun.* **1988**, 285-287.

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5 Solomon, W. *J. Chem. Soc.* **1946**, 934-936.

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7 Typical procedure: Compound **2** (n mmol) was dissolved in n ml glacial acetic acid. Zinc powder (10n mmol) was added and the suspension was heated for 3 hours at 80° C. After cooling and dilution with ether, the mixture was filtered over Celite and the filtrate was washed with aqueous saturated $NaHCO_3$. The solvent was evaporated and the crude product was subjected to recristallisation or column chromatography.

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