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A NOVEL METHOD FOR THE PREPARATION OF VARIOUS 2-PYRIDYL SULFIDES FROM ALCOHOLS

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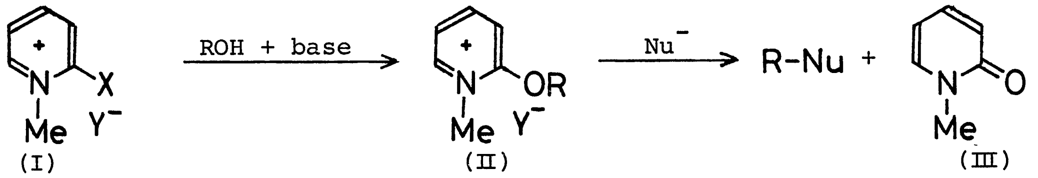
1-Methyl-2-alkoxypyridinium salts, easily formed in situ from 1-methyl-2-fluoropyridinium salt and alcohols, react with pyrid-2-thione in the presence of triethylamine to give the corresponding 2-pyridyl sulfides in good yields.

During the course of our investigation on the synthetic utilization of pyridinium salts[1], it seemed that 1-methyl-2-alkoxypyridinium salt (II) would act as an alkylating reagent on treatment with a nucleophile such as thiol or amine to result in the formation of alkylated product and 1-methyl-2-pyridone (III).



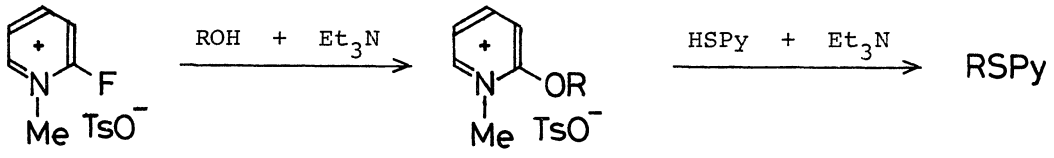
Further it also seemed that the ionic process of this substitution reaction would be entropically advantageous since nucleophile comes in close proximity with the pyridinium salt.

To realize this assumption, the reaction of 1-methyl-2-benzyloxypyridinium p-toluenesulfonate (IIb)[2] with pyrid-2-thione in the presence of triethylamine was examined first, and benzyl 2-pyridyl sulfide was obtained in 86% yield along with 1-methyl-2-pyridone (III).

In the next place, the attention was focused to find a convenient method for the preparation of 1-methyl-2-benzyloxypyridinium salt from 2-halopyridinium salt (I) and benzyl alcohol as a model alcohol. After a number of experiments, it was found that when 1-methyl-2-fluoropyridinium p-toluenesulfonate (Ia)2) was treated with benzyl alcohol and triethylamine in chloroform at room temperature for 1 hr, the consumption of benzyl alcohol was checked by a silica gel thin layer chromatograph, and also the existence of IIb was confirmed by n.m.r. spectrum.3) On the other hand, when 1-methyl-2-chloropyridinium p-toluenesulfonate was used instead of Ia, only a small amount of IIb was formed under the above mentioned condition. Therefore, it is apparent that the use of 1-methyl-2-fluoropyridinium salt (Ia) is essential for the formation of an active intermediate, 1-methyl-2-alkoxypyridinium salt (IIa).

The preparation of various 2-pyridyl sulfides, important intermediates in the synthesis of natural product4), by one step procedure from alcohol was successfully achieved by synthetic scheme illustrated in above equation.

A typical procedure is described for the preparation of benzyl 2-pyridyl sulfide; to a suspended chloroform (1 ml) solution of Ia (1 mmol) was added a mixture of benzyl alcohol (1 mmol) and triethylamine (1 mmol) in chloroform (1 ml) under an argon atmosphere and stirred for 1 hr at room temperature to give a clear yellow solution. Then the solution of pyrid-2-thione (1 mmol) and triethylamine (1 mmol) in chloroform (2 ml) was added successively to the resulting mixture and stirred for 3 hr at room temperature. After evaporation of the solvent, small amount of water was added. An organic layer was extracted with ether, and the extract was condensed under reduced pressure. The residue was chromatographed on silica gel, and benzyl 2-pyridyl sulfide was obtained in 90% yield. The results are summarized in the following Table.



(Ia) (IIa) (IV)

Table The preparation of 2-pyridyl sulfides from alcohols.

Alcohol R	Temperature	Time (hr)	Sulfide (IV)[a)] Yield (%)
$C_6H_5CH_2$	r.t.	3	90
$C_6H_5(CH_3)CH$	r.t.	over night	71
$CH_3CH{=}CHCH_2$	r.t.	3	78
$C_3H_7CH{=}CHCH_2$	r.t.	over night	80
$CH_2{=}CH(CH_3)CH$	r.t.	3	63[b)]
C_2H_5	reflux	8	68
$n\text{-}C_8H_{17}$	reflux	8	80
$C_6H_5CH_2CH_2$	reflux	8	66

a) The structure of the sulfide was confirmed by spectrometric (i.r. and n.m.r.) and gas chromatographic analysis.

b) The product was obtained as a mixture of 1-methyl-2-propenyl 2-pyridyl sulfide and 2-butenyl 2-pyridyl sulfide. The ratio of the two isomers was determined by gas chromatographic analysis as 2 : 1.

As shown in the Table, benzylic and allylic 2-pyridyl sulfides were obtained in good yields at room temperature. While, the other sulfides, such as ethyl, n-octyl or phenethyl 2-pyridyl sulfides, were produced when the reaction mixture was refluxed in chloroform.

Similarly, benzyl phenyl sulfide was prepared in 86% yield from benzenethiol and benzyl alcohol via Ia according to the procedure described in the case of benzyl 2-pyridyl sulfide.

It should be noted that the present process provides a new method for the preparation of various allyl or alkyl sulfides from the corresponding alcohols in good yields by one step procedure.

Further synthetic utilization of 2-alkoxypyridinium salt is now in progress.

REFERENCES

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2) 1-methyl-2-fuluoropyridinium p-toluenesulfonate (Ia) or 1-methyl-2-benzyloxypyridinium p-toluenesulfonate (IIa) was prepared by the reaction of 2-fuluoropyridine or 2-benzyloxypyridine and methyl p-toluenesulfonate.

3) n.m.r. (δ_{TMS} ppm, $CDCl_3$): 2.29 (s, 3H), 4.00 (s, 3H), 5.54 (s, 2H), 6.98～8.87 (m, 13H).

4) K. Narasaka, M. Hayashi, and T. Mukaiyama, Chem. Lett., 259 (1972).

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