CHEMISTRY LETTERS, pp. 381-384, 1976. Published by the Chemical Society of Japan

SYNTHESIS OF UNSYMMETRICAL KETONES BY THE REDUCTION OF 2-ALKOXYPYRIDINIUM SALTS FORMED FROM α-HYDROXY KETONES (ACYLOINS) WITH SODIUM HYDROSULFITE

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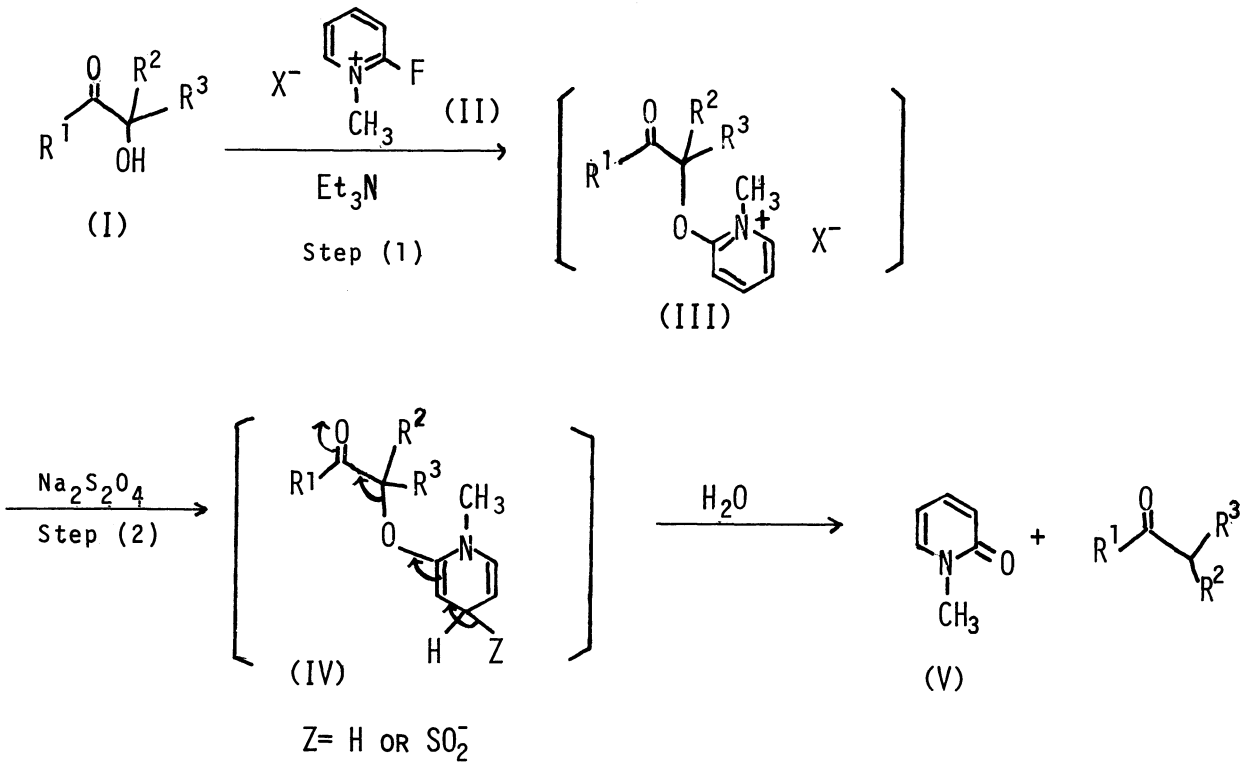
α-Hydroxy ketones (acyloins) were reduced to the corresponding ketones in good yields via pyridinium salts by the successive treatment with 1-methyl-2-fluoropyridinium p-toluenesulfonate and sodium hydrosulfite.

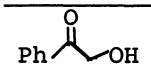
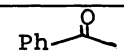
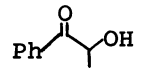
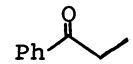
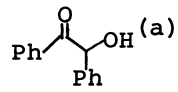
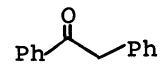
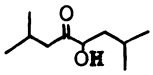
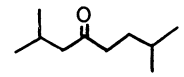
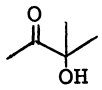
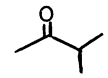
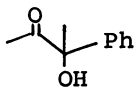
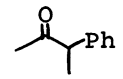
In the preceding papers, it was shown that 2-halopyridinium salts were effectively employed as coupling reagents for the preparations of carboxylic esters, carboxamides, and lactones.[1] It was also found in our laboratory that 1-methyl-2-alkoxypyridinium salts were easily formed in situ from 1-methyl-2-fluoropyridinium salt and alcohols.[2] Further, it is well known that pyridinium salts undergo facile reduction by sodium hydrosulfite to afford 1,4-dihydropyridine derivatives exclusively.[3] Based on these facts, it seemed that 1-methyl-2-(β-keto-alkoxy)-pyridinium salts (III) would be formed in situ by treatment of 1-methyl-2-fluoro-pyridinium salts (II) with α-hydroxy ketones (I). The pyridinium salts (III) thus formed would react with sodium hydrosulfite to give the corresponding 1,4-dihydro-pyridine, which in turn would decompose spontaneously to result in the formation of the corresponding ketones and 1-methyl-2-pyridone (V) as shown in the scheme.[4]



Expectedly, α-hydroxy ketones were reduced in good yields to the corresponding ketones by the successive treatment with 1-methyl-2-fluoropyridinium p-toluenesulfonate and sodium hydrosulfite. General procedure for the reduction of α-hydroxy ketones is shown in the following; to a suspension of 1-methyl-2-fluoropyridinium p-toluenesulfonate (0.566 g, 2 mmol) in dichloromethane (1 ml) under argon atmosphere was added a mixture of 2-hydroxypropiophenone (0.150 g, 1 mmol) and triethylamine (0.202 g, 2 mmol) with stirring at room temperature. The mixture was stirred for 1 hr and then an aqueous solution of sodium hydrosulfite (1.02 g, 5 mmol) was added. The mixture was stirred continuously until it became yellow. The product was extracted with dichloromethane and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was subjected to thin layer chromatography. Propiophenone was separated and obtained in 81% yield.

In a similar manner, several ketones were obtained in good yields by the treatment of α-hydroxy ketones with 1-methyl-2-fluoropyridinium p-toluenesulfonate and sodium hydrosulfite as shown in the Table. However, α-hydroxy ketones having tertiary hydroxy group gave the ketones only in 30-40% yields, and the starting acyloins were recovered.

Table Reduction of α-hydroxy ketones with 1-methyl-2-fluoropyridinium p-toluenesulfonate and sodium hydrosulfite.

α-Hydroxy ketones	Molar ratio[b] (II)	Molar ratio[b] Et_3N	Time(min) (c)	Time(min) (d)	Product*	Yield(%)[e]
	2.0	2.0	50	120		86
	2.0	2.0	60	120		81
 [a]	2.0	2.0	45	120		96
	2.0	2.0	60	120		84[f]
	2.0	2.0	90	120		39[g]
	2.0	2.0	120	120		33

* Structures of products were confirmed by elemental analyses and spectral data compared with authentic samples.

(a) The use of 1-methyl-2-fluoro-3-methylpyridinium p-toluenesulfonate gave a more favarable result than that of 1-methyl-2-fluoropyridinium p-toluenesulfonate. In the latter case, the reduction proceeded sluggishly, since white precipitates appeared soon when benzoin was added to the solution of sulfonate. (b) Optimum yields were recorded when 2 equivalents of the pyridinium salt and triethylamine were employed. About thirty percent of α-hydroxy ketones were recovered when each 1 equivalent of the both reagents was used. (c) Reaction time of step (1). (d) Reaction time of step (2). (e) Isolated yields by preparative tlc (silica gel). (f) Isolated yield by distillation. (g) The yield determined by vpc, using an internal standard.

It is noted that the present procedure provides a convenient method for the preparation of various unsymmetrical ketones starting from carboxylic esters via acyloins.

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2) T. Mukaiyama, S. Ikeda, and S. Kobayashi, Chem. Lett., 1159 (1975).
3) (a) U. Eisner and J. Kuthan, Chem. Rev., 72, 1 (1972).
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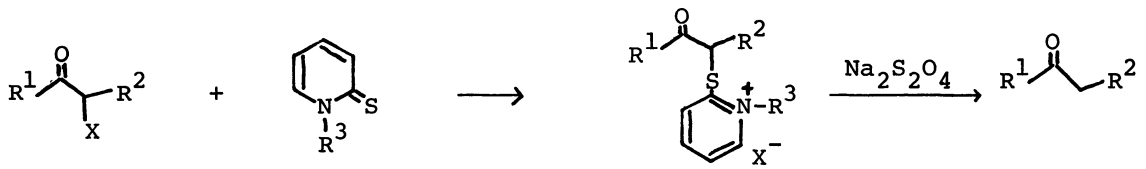
4) A few methods for the reduction of acyloins have been reported.
(a) Org. Syntheses Coll. Vol. 4, 218 (1963).
(b) D. J. Cram and M. Cordon, J. Amer. Chem. Soc., 77, 1810 (1955) and references therein.
(c) Y. Abe, Yukagaku, 20, 224 (1971) (Japan).
5) In the present experiments, it was also found that the reduction of 1-methyl-2-(β-keto-alkylthio)pyridinium halides, produced from 1-methyl-2-pyridothione and α-halo ketones, gave the corresponding ketones in higher yields than the reduction of β-keto-alkylpyridinium salts with sodium hydrosulfite reported by Ho.[3c]



R^1= CH_3, R^2= CH_2Ph, R^3= CH_3,
X= Br: 86%
R^1= Ph, R^2= Ph, R^3= CH_2Ph,
X= Cl: 98%

(Received March 3, 1976)