Tetrahedron Letters No. 13, pp 1237 - 1240, 1972. Pergamon Press. Printed in Great Britain.

THE SYNTHESIS OF 4-ALKYLATED PYRIDINES FROM 4-(1H)-PYRIDONES

Francis X. Smith and Gordon G. Evans

Department of Chemistry, Tufts University

Medford, Massachusetts 02155, U. S. A.

(Received in USA 21 January 1972; received in UK for publication 17 February 1972)

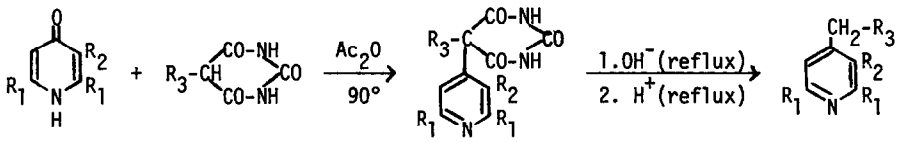
In contrast to the great many reported reactions which involve displacement of leaving groups from the 4-position of the pyridine ring by O-, N-, and S-atom nucleophiles, those using C-atom nucleophiles are relatively few in number and for the most part of limited applicability (1,a-g; 2,a,c). We wish to report a reaction which seems to be of this type and which should have general synthetic utility. Our work bears some resemblance to that of Gebauer (2,a-d), who prepared 5-alkyl-5-(4-pyridyl)barbituric acids by heating 5-alkylbarbituric acids with N-(4-pyridyl)pyridinium salts or 4-bromo- or 4-chloropyridine, and converted these acids in excellent yield to the corresponding 4-alkylpyridines by hydrolysis and decarboxylation; and of Eiden and Peter (3), who prepared pyridone methides by heating 1-phenyl-4-pyridone and several of its derivatives with active methylene compounds in acetic acid-acetic anhydride solution.

We have found that 4-(1H)-pyridone and its 3-methyl and 2,6-dimethyl derivatives react readily with various 5-substituted barbituric acids in acetic anhydride solution at moderate temperatures; the resulting 5-substituted-5-(4-pyridyl)barbituric acids can be converted to the 4-substituted pyridines by the method of Gebauer (Table I). Pyridones, which have the advantages of stability and ready availability by several routes, are desirable starting materials for the synthesis of these products.

The reaction also succeeds when the barbituric acid derivatives are replaced by cyclic isopropylidene esters of alkylmalonic acids, which are of comparable acidity (4). In this case lower temperatures are used in order to minimize decomposition of the reagent esters.

The isopropylidene alkyl(4-pyridyl)malonates can be readily converted not only into

Table I. Reaction of 4-(1H)-Pyridones with 5-Substituted Barbituric Acids

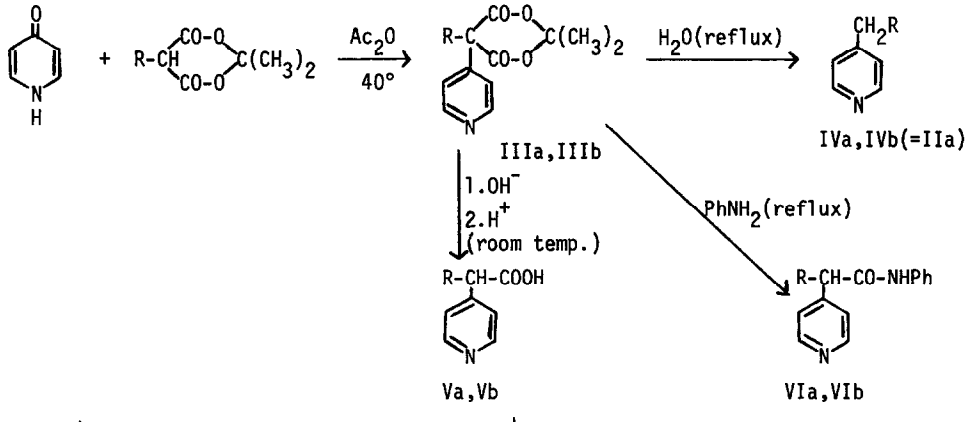


I,a-f II,a-f

	R_1	R_2	R_3	I		II	
				% yield	M.p.	% yield	M.p.
a:	H	H	Butyl	75	258-9d.(EtOH)*	80	Picrate 101-2**(aq.EtOH)
b:	H	H	Phenacyl	80	291-3d.(aq.EtOH)	55	83-4(hexane)
c:	H	H	Allyl	74	266-8d.(EtOH)#	76***	Chloroplatinate 171-3(H_2O)
d:	CH_3	H	Butyl	57	217-18(aq.EtOH)	74	Chloroplatinate 179-81(H_2O)
e:	H	CH_3	Ethyl	69	251-2(aq.EtOH)	51	Picrate 135-7##(EtOH)
f:	H	CH_3	Butyl	68	214-16(aq.EtOH)	64	Picrate 94-5(aq.EtOH)

*Lit. m.p. 260 (2,c). **Lit. m.p. 102-3 (5). #Lit. m.p. 270d. (2,c). ##Lit. m.p. 136-8(6).
***The infrared spectrum confirmed the terminal position of the double bond.

Table II. Reaction of 4-(1H)-Pyridone with Isopropylidene Alkylmalonates



IIIa,IIIb IVa,IVb(=IIa) Va,Vb VIa,VIb

	a (R = ethyl)		b (R = butyl)	
	% yield	M.p.	% yield	M.p.
III	57	133-4(hexane)	40	91-2(hexane)
IV	87	Picrate 129-30*(aq.EtOH)	75	Picrate 102-3(aq.EtOH)
V	77	Hydrochloride 107d.** (EtOH-Et_2O)	84	Na salt >310d.(EtOH-Et_2O)
VI	80	170-1(benzene)	63	125-6(toluene-hexane)

*Lit. m.p. 134 (5). **Loses CO_2 and resolidifies as IVa.HCl.

4-alkylpyridines but also into 2-(4-pyridyl)alkanoic acids and 2-(4-pyridyl)alkanoylanilides (Table II).

EXPERIMENTAL

5-Substituted-5-(4-pyridyl)barbituric acids and subsequent degradation:

An acetic anhydride solution 1 molal in both the 4-pyridone and the 5-substituted barbituric acid* was heated at 90° for two days. The cooled reaction mixture was then dissolved in a large amount of water and a small amount of conc. hydrochloric acid was added to clarify the solution. After filtration, the product was precipitated by adding sodium bicarbonate.

The corresponding 4-alkylpyridine derivative was obtained by refluxing the barbituric acid derivative with seven times its weight of 15% potassium hydroxide solution overnight, then making slightly acidic with hydrochloric or acetic acid and refluxing again overnight. The product was caused to separate by the addition of excess potassium hydroxide. Product IIa was also obtained directly in 80% yield by refluxing Ia with five times its weight of 15% sodium carbonate solution for two days.

Isopropylidene alkyl(4-pyridyl)malonates and subsequent transformations:

4-(1H)-Pyridone (10 mmoles), the isopropylidene alkylmalonate (15 mmoles), and 2 ml. acetic anhydride were warmed at 40° for one week. The solution was then treated with 30 g. ice and 10 drops conc. hydrochloric acid and filtered. Sodium bicarbonate was added to precipitate the product.

The cyclic ester was hydrolyzed with the loss of one carboxyl group by brief stirring in warm 10% sodium hydroxide until a clear solution was obtained followed by acidification at room temperature with hydrochloric acid. The hydrochloride of V,a was obtained by evaporation of the acidic aqueous solution and extraction of the residue with abs. ethanol; filtration and evaporation yielded an oil which crystallized upon the addition of acetone. The sodium salt of V,b was obtained by neutralization of the acidic solution with excess sodium bicarbonate, evaporation to dryness, extraction of the residue with abs. ethanol, filtration and evaporation.

The alkanoylanilide was prepared by refluxing the cyclic ester with three times its weight of aniline for one hour, cooling, and diluting with an ether-hexane mixture.

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* 5-Phenacylbarbituric acid, m.p. 236-7 (EtOH), a new compound, was prepared in 56% yield by refluxing phenacyl bromide and barbituric acid in aqueous ethanol containing sodium acetate.

The 4-alkylpyridine was produced as an insoluble oil by refluxing the cyclic ester with four times its weight of water for one day.

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ACKNOWLEDGMENT. We are grateful to Mr. James R. Joiner and Mr. William H. Koster for assistance in characterizing some of the products.