[Contribution No. 975 from the Department of Chemistry, University of Pittsburgh]

The Synthesis of Nitrogen-Containing Ketones. VI. The Acylation of 2-Ethyl- and 2-Isobutyl-pyridine[1,2]

CARL OSUCH[3] AND ROBERT LEVINE

Received April 11, 1956

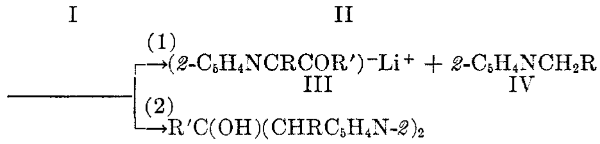
2-Ethyl- and 2-isobutyl-pyridine have been acylated with a series of esters using phenyllithium as the condensing agent to give ketones, 2-$C_5H_4NCHRCOR'$, or mixtures of ketones and carbinols, $R'C(OH)(CHRC_5H_4N\text{-}2)_2$ ($R{=}CH_3$ or $i\text{-}C_3H_7$) depending on the nature of R and R′. Methyllithium and sodium amide have been used to effect the benzoylation of 2-methyl- and 2-ethyl-pyridine but these condensing agents are not as effective as phenyllithium.

Relatively few ketones of the type 2-$C_5H_4NCHRCOR'$ (2-C_5H_4N = 2-pyridyl, R = alkyl and R′ = alkyl or aryl), I, are reported in the literature. For example, 3-(2-pyridyl)-2-heptanone (I, R = $n\text{-}C_4H_9$ and R′ = CH_3) was prepared in 10% yield by the interaction of 2-*n*-amylpyridine, phenyllithium, and acetonitrile followed by hydrolysis of the resulting ketimine.[4] In addition, the syntheses of four ketones of type I (R = alkyl and R′ = phenyl) have been accomplished by the sodium amide-effected alkylations of 2-phenacylpyridine with alkyl halides.[5,6]

The present report is concerned with the preparation of a series of ketones of type I where R = CH_3 or $i\text{-}C_3H_7$ and R′ = alkyl, aryl, or heterocyclic. The method used involves the interaction of two equivalents of the lithium derivatives of 2-ethyl- or 2-isobutyl-pyridine, prepared from the alkyl pyridine and phenyllithium, with one equivalent of the appropriate ester—a method we have used successfully for the acylation of certain tar bases containing a methyl group in the 2-position of the heterocyclic ring.[7-9]

Our results are summarized in Table I. It will be noticed that when the acylating ester is aromatic or heterocyclic only ketones are formed regardless of whether 2-ethyl- or 2-isobutyl-pyridine is acylated. However, when the acylating ester is aliphatic, either ketones or mixtures of ketones and carbinols may be obtained depending on the structures of both the 2-alkylpyridine and the acylating ester.

It appears that when a 2-alkylpyridine is acylated using an organolithium compound as the condensing agent, the ketone (I) which is prepared may react further[7] in two ways with part of the initially-formed lithium derivative of the alkylpyridine, II.



$$\underset{\text{I}}{2\text{-}C_5H_4NCHRCOR'} + \underset{\text{II}}{(2\text{-}C_5H_4NCHR)^-Li^+} \longrightarrow$$

$$\xrightarrow{(1)} \underset{\text{III}}{(2\text{-}C_5H_4NCRCOR')^-Li^+} + \underset{\text{IV}}{2\text{-}C_5H_4NCH_2R}$$

$$\xrightarrow{(2)} \underset{\text{V}}{R'C(OH)(CHRC_5H_4N\text{-}2)_2}$$

Apparently when R = CH_3 or $i\text{-}C_3H_7$ and R′ = C_6H_5 or 4-C_5H_4N, the methinyl hydrogen atom of I is still sufficiently acidic so that the acid-base reaction (1), with the formation of anion III, is the only reaction which occurs. However, when R′ is aliphatic, the methinyl hydrogen atom of I is probably less acidic than when R′ is aromatic or heterocyclic and it may be anticipated that I and II may react by both an acid-base reaction (scheme 1) and by carbonyl addition (scheme 2) to give carbinol, V.

When R = CH_3 and R′ is increased in size from methyl to ethyl to isopropyl, it may be seen that the yield of ketone increases at the expense of the carbinol and that when R′ = $i\text{-}C_3H_7$, apparently the carbonyl group of I is sufficiently sterically hindered so that the anion of 2-ethylpyridine cannot add to it. Furthermore, the carbonyl group of the ketone (I, R = $i\text{-}C_3H_7$ and R′ = CH_3), formed by acylating 2-isobutylpyridine with methyl acetate, appears to be sufficiently hindered so that a high yield (70.8%) of ketone and only a very low yield (3.2%) of carbinol are obtained, while increasing the size of R′ to ethyl or isopropyl leads to the complete exclusion of carbinol formation.

It is interesting to note that the attempted acylation of 2-isopropylpyridine with methyl benzoate gave none of the expected ketone, 2-$C_5H_4NC(CH_3)_2COC_6H_5$. Instead, there was obtained a 21% yield of triphenylcarbinol which was formed by the interaction of the ester with the condensing agent, phenyllithium. These results are not too surprising

---

[1] This work was performed under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

[2] For paper V in this series, see Miller, Osuch, Goldberg, and Levine, *J. Am. Chem. Soc.*, **78**, 674 (1956).

[3] This paper is based in part on the thesis presented by Carl Osuch to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree; present address: Monsanto Chemical Co., St. Louis, Missouri.

[4] Burger and Ullyot, *J. Org. Chem.*, **12**, 342 (1947).

[5] Sperber, Fricano, and Papa, *J. Am. Chem. Soc.*, **72**, 3068 (1950).

[6] Beckett and Kerridge, *J. Chem. Soc.*, 2948 (1954).

[7] Goldberg, Barkley, and Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

[8] Goldberg and Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

[9] Goldberg and Levine, *J. Am. Chem. Soc.*, **77**, 3647 (1955).

TABLE I

THE PHENYLLITHIUM-EFFECTED ACYLATIONS OF 2-ETHYL- AND 2-ISOBUTYLPYRIDINE WITH ESTERS

	Ketone, 2-PyCHRCOR′						Analysis						Monopicrate			
			Yield,	B.P.			Calc'd			Found					Nitrogen	
Ester, Methyl	R	R′	%	°C.	mm.	Formula	C	H	N	C	H	N	M.P., °C.	Formula	Calc'd	Found
Benzoate	CH_3	C_6H_5	67.8	163–164[h]	5	$C_{14}H_{13}NO$			6.63			6.61	162.4–163.1	$C_{20}H_{16}N_4O_8$	12.73	12.79
	i-C_3H_7	C_6H_5	82.4	135–142	1.5	$C_{16}H_{17}NO$			5.85			5.98	133.9–134.7	$C_{22}H_{20}N_4O_8$	11.96	11.84
Isonicotinate	CH_3	4-Py[a]	73.5	131–133	1	$C_{13}H_{12}N_2O$	73.56	5.70		73.68	5.97		186.2–187.2	$C_{19}H_{15}N_5O_8$	15.87	16.11
	i-C_3H_7	4-Py[a]	69.2	140–141	1	$C_{15}H_{16}N_2O$	74.97	6.71		74.54	6.47		186.6–188.0[b]	$C_{27}H_{22}N_8O_{15}$	16.04	15.99
Acetate	CH_3	CH_3	52.4[c]	96–97	7.1	$C_9H_{11}NO$			9.38			9.41	111.1–113	$C_{15}H_{14}N_4O_8$	14.82	14.87
	i-C_3H_7	CH_3	70.8[d]	105–111	9	$C_{11}H_{15}NO$			7.90			8.19	117.8–119	$C_{17}H_{18}N_4O_8$	13.79	13.71
Propionate	CH_3	C_2H_5	65.3[e]	83–85	2.1	$C_{10}H_{13}NO$			8.58			8.73	108.0–109.8[f]	$C_{16}H_{16}N_4O_9$	13.72	14.07
	i-C_3H_7	C_2H_5	67.2	86–88	1.8	$C_{12}H_{17}NO$			7.32			7.04	99.8–100.6	$C_{18}H_{20}N_4O_8$	13.33	13.74
Isobutyrate[g]	CH_3	i-C_3H_7	71.7	75–77.5	1.3	$C_{11}H_{15}NO$	74.54	8.53		74.29	8.26		114.8–115.6	$C_{17}H_{18}N_4O_8$	13.79	14.16
	i-C_3H_7	i-C_3H_7	63.7	83–87	1.7	$C_{13}H_{19}NO$	76.05	9.33		75.92	8.96		121.0–122.3	$C_{19}H_{22}N_4O_8$	12.90	13.22

[a] 4-Py is the 4-pyridyl radical. [b] This is a dipicrate. [c] There was also obtained a 19.7% yield of the carbinol, 3-methyl-2,4-di-(2-pyridyl)-3-pentanol, b.p. 162–164° at 2.3 mm. *Anal.* Calc'd for $C_{16}H_{20}N_{20}$: N, 10.93. Found: 10.66. [d] There was also obtained a 3.2% yield of the carbinol, 2,4,6-trimethyl-3,5-di-(2-pyridyl)-4-heptanol, b.p. 144–150° at 1 mm. This carbinol gave a *dipicrate*, m.p. 177.3–178.0°. *Anal.* Calc'd for $C_{32}H_{34}N_8O_{15}$: N, 14.56. Found: N, 14.79. [e] There was also obtained 3.3% of the crude carbinol, 3-ethyl-2,4-di-(2-pyridyl)-3-pentanol, b.p. 124–140° at 1.3 mm. This carbinol gave a *dipicrate*, m.p. 169.0–169.6°. *Anal.* Calc'd for $C_{29}H_{28}N_8O_{15}$: N, 15.38. Found: N, 15.54. [f] This is a *styphnate.* This compound also gave a *trinitro-m-cresolate*, m.p. 105.5–107.0°. *Anal.* Calc'd for $C_{17}H_{18}N_4O_8$: N, 13.79. Found: N, 13.34. [g] This is the ethyl ester. [h] Substance has m.p. 67.2–68.2°.

since Doering and Pasternak[10] have found that 2-*sec*-butylpyridine which, like 2-isopropylpyridine, has a methinyl carbon atom attached to the 2-position of the pyridine ring is not metalated by either phenyllithium or sodium triphenylmethide.

The benzoylations of 2-methyl- and 2-ethyl-pyridine were also effected using both sodium amide in liquid ammonia and methyllithium in ether as the condensing agents. These results are found in Table II, in which the data obtained in the comparable acylations using phenyllithium as the condensing agent are included for purposes of comparison. It can be seen that phenyllithium is the most effective of the three condensing agents studied since it gives the highest yields of products. It can also be seen that the formation of the anion of 2-methylpyridine by its reaction with methyllithium appears to be time dependent. Thus, as the time allowed for anion formation is increased from one-half to one to two hours, the yield of 2-phenacylpyridine is increased from 48% to 52% to 61%. A further increase in anion formation time to four hours has no effect on the yield of product. That unreacted methyllithium was present when methyl benzoate was added to an ether solution of methyllithium and 2-methylpyridine which had been refluxed for 30 minutes was shown by the fact that in addition to 2-phenacylpyridine (48.4%), small amounts of acetophenone and α-methylstyrene were also obtained. The latter two products no doubt arise from the interaction of methyl benzoate with one and two moles of methyllithium respectively.

$$C_6H_5CO_2CH_3 + CH_3Li \longrightarrow \underset{\text{VI}}{C_6H_5COCH_3} + LiOCH_3$$

$$\text{VI} + CH_3Li \longrightarrow C_6H_5C(OH)(CH_3)_2 \xrightarrow{-H_2O} C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH_2$$

Finally it should be pointed out that Weiss and Hauser[11] have previously benzoylated 2-methylpyridine in 47–57% yields using potassium amide as the condensing agent and a reaction time of five to ten hours. In the present study this reaction has been effected in 50% yield using the less costly reagent, sodium amide, and a considerably shorter total reaction time of approximately two hours.

EXPERIMENTAL[12]

In this section four typical experiments are described in detail.

The acylation of 2-ethylpyridine with methyl acetate using phenyllithium as the condensing agent. 2-Ethylpyridine (42.9 g., 0.4 mole), dissolved in 50 ml. of anhydrous ether, was

---

(10) Doering and Pasternak, *J. Am. Chem. Soc.*, **72,** 143 (1950).

(11) Weiss and Hauser, *J. Am. Chem. Soc.*, **71,** 2023 (1949).

(12) The 2-methyl- and 2-ethylpyridine used in this study were supplied through the courtesy of Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

added over a period of 15–20 minutes to a solution of 0.4 mole of phenyllithium [prepared from lithium ribbon (5.6 g., 0.8 mole) and bromobenzene (42.9 g., 0.4 mole)] in 400 ml. of anhydrous ether and the mixture then was refluxed for 30 minutes. The ether solution of lithio-2-ethylpyridine is dark red in color. Methyl acetate (14.8 g., 0.2 mole), dissolved in 25 ml. of anhydrous ether, was added at such a rate that the ether refluxed gently. The mixture was refluxed for an additional 30 minutes after the ester was added. Then it was allowed to cool to room temperature and was poured onto 300–400 g. of crushed ice and 100 ml. of concentrated hydrochloric acid. The layers were separated and the ether layer was extracted with several 100-ml. portions of 6 *N* hydrochloric acid. This treatment results in the separation of the neutral from the basic materials. The combined acid extracts were made slightly basic by the addition of solid sodium carbonate and then were extracted with several portions of ether. The combined ether extracts were dried over sodium sulfate and then were distilled first at atmospheric pressure and then in a vacuum to give 15.6 g. (52.4%) of 3-(2-pyridyl)-2-butanone, b.p. 96–97° at 7.1 mm. and 10.1 g. (19.7%) of 3-methyl-2,4-di-(2-pyridyl)-3-pentanol, b.p. 162–164° at 2.3 mm. The analytical data for these compounds appear in Table I.

Attempted acylation of 2-isopropylpyridine with methyl benzoate using phenyllithium as the condensing agent. This experiment was performed using the procedure described above except that 0.1 mole of phenyllithium was used, the 2-ethylpyridine was replaced by 2-isopropylpyridine (12.1 g., 0.1 mole), and the methyl acetate was replaced by methyl benzoate (13.6 g., 0.1 mole). On processing the reaction mixture, the only basic compound isolated was 6.0 g. (50%) of recovered 2-isopropylpyridine, b.p. 150–156° at 726 mm. From the phase containing the neutral material, there were obtained 6.4 g. (47%) of recovered methyl benzoate, b.p. 80–85° at 15.5 mm., and 2.8 g. (21.5%) of triphenylcarbinol, m.p. 160–161° alone and when mixed with an authentic sample.

The benzoylation of 2-methylpyridine (a) using methyllithium as the condensing agent. Methyllithium was prepared in 95% yield by the interaction of lithium (4.2 g., 0.6 mole) and methyl iodide (42.6 g., 0.3 mole) in 400 ml. of anhydrous ether. To this solution, 2-methylpyridine (26.5 g., 0.285 mole), dissolved in 30 ml. of anhydrous ether, was added over a period of 25 minutes and was followed, after a one-half hour reflux period, by the addition of methyl benzoate (19.4 g., 0.142 mole), dissolved in 25 ml. of anhydrous ether. The mixture was refluxed for an additional 30 minutes and then was processed in the customary manner. From the basic phase there was obtained 13.6 g. (48.4%) of 2-phenacylpyridine, b.p. 144–148° at 1.5 mm.,[7] m.p. 52.5–54°;[7] *picrate, m.p.* 181–182°.[13] Distillation of the neutral phase at atmospheric pressure gave 2.3 g. of material boiling at 150–190°, 5.8 g. (30%) of recovered methyl benzoate (b.p. 190–200°), and 1.0 g. of acetophenone (b.p. 200–204°; *2,4-dinitrophenylhydrazone,* m.p. 248–249° alone and when mixed with an authentic sample). The material boiling at 150–190° decolorizes a solution of bromine in carbon tetrachloride and was shown to contain α-methylstyrene since its reduction with sodium in absolute ethanol gave isopropylbenzene; m.p. of the *p-sulfonamide* was 105.3–106°[14] alone and when mixed with an authentic sample.

(*b*) *Using sodium amide as the condensing agent.* A suspension of sodium amide (0.4 mole) in 300 ml. of anhydrous ammonia was prepared as described by Adams and Hauser.[15] Undiluted 2-methylpyridine (37.2 g., 0.4 mole) was added and the resulting reddish-orange mixture was stirred for 15–20 minutes. Methyl benzoate (27.2 g., 0.2 mole), dissolved in 35 ml. of anhydrous ether, was added over a period of 25–35 minutes; the reaction mixture was stirred for an additional hour and then the reaction was quenched by the addition of solid ammonium chloride. The liquid ammonia was removed by warming the reaction mixture on a water-bath and was replaced by ether. When the liquid ammonia had evaporated as indicated by the refluxing of the ether, the reaction mixture was poured onto crushed ice and made strongly acidic with concentrated hydrochloric acid. The mixture then was processed as described in the first experiment above to give 19.8 g. (50.2%) of 2-phenacylpyridine, b.p. 144–148° at 1.5 mm.,[7] m.p. 52–54°.[7]

TABLE II

BENZOYLATION[a] OF 2-METHYL- AND 2-ETHYL-PYRIDINE USING VARIOUS CONDENSING AGENTS

Alkylpyridine 2-C_5H_4NR R	Condensing Agent	Anion Formation Time in Hours[b]	Ketone 2-$C_5H_4NCHR'COC_6H_5$	
			R′	Yield,[c] %
CH_3	C_6H_5Li	0.5	H	81.8[d]
C_2H_5	C_6H_5Li	0.5	CH_3	67.8[f]
CH_3	CH_3Li	0.5	H	48.4[e]
		1.0	H	52.0[e]
		2.0	H	61.2[e]
		4.0	H	61.2[e]
C_2H_5	CH_3Li	0.5	CH_3	25.5[f]
CH_3	$NaNH_2$	0.25	H	50.2[e]
C_2H_5	$NaNH_2$	0.25	CH_3	42.2[f]

[a] Methyl benzoate was used as the acylating agent in all cases. [b] This refers to the reflux period after all the tar base had been added to the condensing agent but before the addition of the acylating ester. After the ester was added, the mixtures were refluxed for one-half hour longer when organolithium compounds were used as condensing agents or stirred for one hour when sodium amide was the condensing agent. [c] In all cases the molar ratio of basic condensing agent, 2-alkylpyridine and ester used was 2:2:1 respectively and the yields were calculated on the molar quantity of ester used. [d] This yield was obtained by Goldberg, Barkley, and Levine (see ref. 7). [e] The constants of this material (b.p. 144–148° at 1.5 mm., m.p. 52.5–54°) agree with those in ref. 7. [f] The constants of this material agree with those found in Table I.

PITTSBURGH 13, PENNSYLVANIA

---

(13) Howton and Goldberg, *J. Org. Chem.*, **15**, 1 (1950).

(14) Tiffeneau, *Compt. rend.*, **134**, 845 (1902).

(15) Adams and Hauser, *J. Am. Chem. Soc.*, **66**, 1220 (1944).