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Alkylation of 3-Picoline[1,2]

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3-Picoline has been alkylated with a number of alkyl halides in liquid ammonia solution using a 2:2:1 molar ratio of 3-picoline:potassium amide:alkyl halide. Observations have been made which appear to indicate that the order of metalation of 3-picoline by the alkali amides is $LiNH_2 < NaNH_2 < KNH_2$.

The hydrogen atoms of the methyl groups in 2-picoline and its vinylogue, 4-picoline, are labile because they may participate in resonance with the azomethine linkage of the pyridine ring. Thus, it has been possible to effect the side chain metalation of these tar bases by treating them with alkali amides and certain organolithium compounds under appropriate reaction conditions. These alkali metal derivatives have been alkylated[3,4] and acylated[5-8] with a large variety of alkyl halides and esters to give compounds of the types 2- and 4-$C_5H_4NCH_2R$ and 2- and 4-$C_5H_4NCH_2COR$.

In 1951, Brown and Murphey[9] elegantly demonstrated that 3-picoline also shows prototropic activity[10] when they found that the interaction of 3-picoline, sodium amide, and methyl chloride in liquid ammonia solution gives 3-ethylpyridine, which may be further methylated to give 3-isopropyl- and 3-*t*-butylpyridine. We have recently shown[11] that 3-picoline may be acylated with aromatic and heterocyclic esters using potassium amide in liquid ammonia[12] as the condensing agent and, thus, a series of the previously unknown ketones containing the 3-pyridyl radical has been made available. The structure of one of these ketones, 3-phenacylpyridine, was established by reducing it to 3-(2-phenylethyl)-pyridine and showing that the properties of the reduction product are identical with those of an authentic sample which was prepared in very low yield (7.7%)[13] by the reaction of 3-picoline, potassium amide, and benzyl chloride.

Because Brown and Murphey[9] had obtained a good yield of product on methylating 3-picoline and we obtained a poor yield on its benzylation, it was of interest to determine what yields of alkylated products would be obtained with a variety of alkyl halides.[14]

For purposes of arriving at the best reaction conditions for effecting the alkylation of 3-picoline, a study was made of its reaction with *n*-butyl bromide. The results obtained are summarized in Table I. It may be seen that the best yield of 3-*n*-amylpyridine (72%) is obtained by the interaction of a 2:2:1 molar ratio of potassium amide, 3-picoline and *n*-butyl bromide for 3 hr. These conditions are superior to both the use of a 2:2:1 molar ratio of reactants for a 35-min. reaction time and a 1:1:1 molar ratio of reactants for a 3-hr. reaction time. Furthermore, when the optimum reaction conditions with potassium amide were used with lithium amide and sodium amide, considerably lower yields of product, *i.e.*, 33.6% and 58.8%, were obtained. These results appear to indicate that the order of metalation of 3-picoline by the alkali amides is lithium amide < sodium amide < potassium amide.[15]

The alkylations, summarized in Table II, were then effected using a 2:1 molar ratio of 3-picolylpotassium to alkyl halide. It should be noted that

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

(3) For leading references, see "The Chemistry of the Alkali Amides. III," by R. Levine and W. C. Fernelius, *Chem. Revs.* **54**, 540 (1954).

(4) C. Osuch and R. Levine, *J. Am. Chem. Soc.*, **78**, 1723 (1956).

(5) M. S. Weiss and C. R. Hauser, *J. Am. Chem. Soc.*, **71**, 2023 (1949).

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(7) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

(8) J. W. Hey and J. P. Wibaut, *Rec. trav. chim.*, **72**, 522 (1953).

(9) H. C. Brown and W. A. Murphey, *J. Am. Chem. Soc.*, **73**, 3308 (1951).

(10) This activity is apparently due to the operation of a powerful inductive effect.

(11) A. D. Miller, C. Osuch, N. N. Goldberg, and R. Levine, *J. Am. Chem. Soc.*, **78**, 674 (1956).

(12) The use of sodium amide gives considerably lower yields.

(13) An 18.3% yield of the dibenzylated product, dibenzyl-3-pyridylmethane was also obtained in this reaction.

(14) While our work was in progress, H. L. Lochte and E. N. Wheeler [*J. Am. Chem. Soc.*, **76**, 5548 (1954)] reported a 16% yield of 3-(cyclopentylmethyl)-pyridine from the interaction of a 1.2:1:1 molar ratio of 3-picoline, sodium amide, and cyclopentyl chloride. After our study had been completed, a paper appeared by E. Hardegger and E. Nikles [*Helv. Chim. Acta*, **39**, 505 (1956)] which reported the alkylation of 3-picoline with four alkyl halides, but only the yield of 3-*n*-butylpyridine (67%) was reported.

(15) In this connection, M. Hamell and R. Levine [*J. Org. Chem.*, **15**, 162 (1950)] have observed that ethyl phenylacetate is self-condensed in considerably lower yield by lithium amide than by sodium amide. Also, H. Gilman, M. W. Van Ess, H. B. Willis, and C. G. Stuckwisch [*J. Am. Chem. Soc.*, **62**, 2606 (1941)] have found that ethyllithium, ethylsodium, and ethylpotassium metalate benzofuran with increasing ease.

TABLE I

USE OF ALKALI AMIDES TO EFFECT ALKYLATION OF 3-PICOLINE WITH *n*-BUTYL BROMIDE

Amide	Moles of Reactants: 3-Picoline	Amide	*n*-Butyl bromide	Reaction Time	% Yield of 3-$C_5H_4NC_5H_{11}$-*n*
Lithium	2	2	1	3 hr.[a]	33.6
Sodium	2	2	1	3 hr.[a]	58.8
Potassium	2	2	1	3 hr.[a]	72.0
	2	2	1	35 min.[b]	60.8
	1	1	1	3 hr.[a]	44.3

[a] The alkali amide and 3-picoline were stirred for 2 hr. The *n*-butyl bromide was then added and stirring was continued for 1 more hr. [b] Anion formation time was 15 min. and stirring time after addition of the halide was 20 min.

TABLE II

3-ALKYLPYRIDINES, 3-$C_5H_4NCH_2R$, BY ALKYLATING 3-PICOLINE WITH ALKYL HALIDES IN THE PRESENCE OF POTASSIUM AMIDE

R	Alkyl Bromide	Yield, %	b.p. or m.p.[a] °C	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_2H_5	Ethyl	49.6	182–184	753	$C_8H_{11}N$	79.29	78.72	9.15	9.17
	Picrate		99.8–100.4[d]		$C_{14}H_{14}N_4O_7$	48.00	48.16	4.03	3.83
C_3H_5	Allyl[b]	13.7	99–102	25	$C_9H_{11}N$	81.15	80.36	8.33	8.36
	Picrate		90.6–91		$C_{15}H_{14}N_4O_7$	49.72	49.90	3.89	3.59
C_3H_7	*n*-Propyl	60.3	75–76	7.5	$C_9H_{13}N$				
	Picrate		88–89[e]		$C_{15}H_{16}N_4O_7$				
C_3H_7	Isopropyl	61.1	85.5–87.5	19	$C_9H_{13}N$	79.95	79.81	9.69	9.70
	Picrate		111.6–112		$C_{15}H_{16}N_4O_7$	49.44	49.84	4.43	4.07
C_4H_9	*n*-Butyl	72.0	110–112	20	$C_{10}H_{15}N$	80.48	80.54	10.13	10.66
	Picrate		78.8–79.2[f]		$C_{16}H_{18}N_4O_7$	50.79	51.14	4.79	4.57
C_4H_9	Isobutyl	46.0	107–108	20	$C_{10}H_{15}N$	80.48	80.19	10.13	10.28
	Picrate		105–105.8		$C_{16}H_{18}N_4O_7$	50.79	50.98	4.79	4.31
$C_4H_{10}N$	β-Dimethylaminoethyl[c]	34.2	101–103	4	$C_{10}H_{16}N_2$	73.06	73.17	9.74	10.08
	Dipicrate		161.6–162.2		$C_{22}H_{22}N_8O_{14}$[g]	42.44	42.21	3.54	3.33
C_5H_9	Cyclopentyl	38.8	149–151	35	$C_{11}H_{15}N$				
	Picrate[h]		120.5–121.5		$C_{17}H_{18}N_4O_7$				
C_5H_{11}	*n*-Amyl	69.6	128–129	20	$C_{11}H_{17}N$	80.92	80.76	10.50	10.24
	Picrate		72.4–73.0[i]		$C_{17}H_{20}N_4O_7$	52.03	52.54	5.14	4.80
$C_6H_{14}N$	β-Diethylaminoethyl[c]	56.3	111–112	3	$C_{12}H_{20}N_2$	74.94	74.87	10.48	10.58
	Dipicrate		141.6–142		$C_{24}H_{26}N_8O_{14}$	44.30	44.75	4.03	3.97

[a] All boiling points and melting points are uncorrected. [b] Chloride was used. [c] Aminochloride hydrochloride was used. In order to free the amine from its hydrochloride, a 3:1 molar ratio of 3-picolylpotassium to hydrochloride was used. In all the other reactions a 2:1 molar ratio of reactants was employed. [d] Hardegger and Nikles (see ref. 14) report 99–100°; [e] a value of 90–90.5° is reported in ref. 17 and a value of 88–89° is given by Hardegger and Nikles (see footnote *d*). [f] Reported value (see footnote *d*) is 77–78°; [g] *N*, calcd.: 18.00; found: 18.04. [h] The styphnate, m.p. 147.5–148.2°, and the trinitro-*m*-cresolate, m.p. 137.8–138.3°, were also prepared. The melting points of all three derivatives agree with those previously reported by Lochte and Wheeler (see ref. 14). [i] Reported value (see footnote *d*) is 71–72°.

by the present method a 38.8% yield of 3-(cyclopentylmethyl)pyridine was obtained as contrasted with the previously reported[14] yield of 16%. Furthermore, while, by the present procedure, 3-picoline is alkylated with *n*-butyl bromide to give a 72% yield of 3-*n*-amylpyridine IV, this compound was previously obtained by Harris *et al.*[16] in an over-all yield of 13.6% by the following multistage synthesis: $CH_3CO_2C_2H_5$ + 3-$C_5H_4NCO_2C_2H_5$ (Claisen) → 3-$C_5H_4NCOCH_2CO_2C_2H_5$(I); I + *n*-C_3H_7Br → 3-$C_5H_4NCOCH(n\text{-}C_3H_7)CO_2C_2H_5$ (II). II (cleavage) → 3-$C_5H_4NCOC_4H_9$-*n*(III); III (Wolff-Kishner) → 3-$C_5H_4NC_5H_{11}$-*n*(IV). In addition, while we have prepared 3-*n*-butylpyridine in 60.3% yield, this compound has been obtained previously[17] in an over-all yield of 24% by the Wolff–Kishner reduction of *n*-propyl 3-pyridyl ketone, which in turn was synthesized from *n*-propylmagnesium bromide and the difficultly accessible 3-cyanopyridine.

EXPERIMENTAL[18]

In this section one typical alkylation is described in detail. *Synthesis of 3-n-Amylpyridine.* 3-Picoline (0.4 mole, 37.2 g.) was added over a 15-min. period to a solution of potas-

(16) G. H. Harris, R. S. Shelton, M. G. VanCampen, E. R. Andrews, and E. L. Schumann, *J. Am. Chem. Soc.*, **73**, 3959 (1951).

(17) R. L. Frank and C. Weatherbee, *J. Am. Chem. Soc.*, **70**, 3482 (1948).

(18) The 3-picoline used in this study was supplied through the courtesy of Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

sium amide, which was prepared from potassium (0.4 mole, 15.6 g.) and 350–400 ml. of anhydrous liquid ammonia. The resulting blood-red mixture was stirred for 2 hr. and then *n*-butyl bromide (0.2 mole, 27.4 g.), diluted with an equal volume of anhydrous ether, was added over a 20-min. period. After the halide was added, the mixture was stirred for an additional hour and then the reaction was quenched by the addition of solid ammonium chloride (0.41 mole, 22.0 g.). The mixture was then processed as described previously for the acylation of 3-picoline[11] to give 1.8 g. of *n*-butyl bromide, 15.5 g. of recovered 3-picoline, b.p. 135–143°, and 21.5 g. (72%) of 3-*n*-amylpyridine, b.p. 110–112° at 20 mm.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Conjugate Additions of Grignard Reagents to α,β-Unsaturated Esters

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The reactions of *sec*-butyl esters of certain α,β-unsaturated acids with Grignard reagents have been studied. In the presence of catalytic amounts of cuprous chloride, Grignard reagents from a number of primary bromides (as well as bromobenzene) add in high yields to the double bond of *sec*-butyl crotonate. This provides a practical route to 3-methylalkanoic acids. The Grignard reagents from isopropyl bromide and *tert*-butyl chloride give lower yields under the same conditions. When no catalyst is used the yield is low, and a higher-boiling condensation-addition product is formed. Condensation products are the only isolated compounds from the cuprous chloride catalyzed reaction with *sec*-butyl methacrylate and tiglate. With *sec*-butyl cinnamate a fair yield of 3-phenylheptanoic ester is obtained with *n*-butylmagnesium bromide, while methylmagnesium bromide gives 4-phenylpentanone-2 as a result of both 1,2- and 1,4-addition. When ferric chloride is used as a catalyst very little 1,4-addition takes place and a dimer of the crotonic ester is formed in varying yields.

The addition of Grignard reagents to carbon-carbon double bonds conjugated with polar double bonds has been the subject of many investigations. Although the 1,4- addition products are generally obtained in moderate to good yields from α,β-unsaturated esters which carry strongly electron-withdrawing groups such as carbalkoxy and cyano groups at the α-carbon,[2–6,23] the yields with other α,β-unsaturated esters have varied widely. Kohler and Heritage[7] have reported that ethyl cinnamate gives exclusively 1,2- addition (dimethylcinnamylcarbinol) with methylmagnesium iodide, but predominantly 1,4- addition (ethyl β,β-diphenylpropionate) with phenylmagnesium bromide. They also found that with increasing size of the alcohol moiety in the cinnamic ester, the rate of 1,4- to 1,2-addition of phenylmagnesium bromide increased, and Hauser *et al.*[8] have reported that with *tert*-butyl cinnamate only the 1,4- addition product is formed. Ethyl α-methylcinnamate[9] and ethyl α-methyl-β-phenylcinnamate[10] give predominantly 1,2- addition with phenylmagnesium bromide, while ethyl α-phenylcinnamate gives exclusively 1,4-addition.[11] Methylmagnesium halides appear to give 1,2-addition in all cases except with the alkylidenemalonic and -cyanoacetic esters. Ethyl crotonate is likewise reported[12] to give crotyldimethylcarbinol with methylmagnesium bromide. It is reported[13] that the Grignard reagent from 2-bromothiophene with ethyl crotonate gives 1,3-di-(2-thenyl)butanone-1 as a result of both 1,2- and 1,4- addition, and the reaction between ethyl methacrylate and methylmagnesium iodide is likewise reported[14] to give both 1,2- and 1,4- addition.

Recently Wotiz *et al.*[15] reported 1,4- addition in up to 40% yield of ethyl-, *tert*-butyl- and phenylmagnesium halides to free crotonic and cinnamic acids. Although we have been able to verify the result reported for the addition of phenylmagnesium bromide to crotonic acid, we have obtained only a low yield (10% or less) of 3-methylheptanoic acid from *n*-butylmagnesium bromide and crotonic acid; large amounts of unidentified nonacidic and high-boiling acidic products are produced.

Since it may be considered established [*e.g.* in

(1) On leave of absence from the Department of Organic Chemistry, The Technical University of Denmark, Sølvgade 83, Copenhagen, Denmark.

(2) Kohler and Reimer, *Am. Chem. J.*, **33**, 333 (1905) [*Chem. Zentr.*, I, 1389 (1905)]; Kohler, *Am. Chem. J.*, **34**, 132 (1905) [*Chem. Zentr.*, II, 1021 (1905)].

(3) Alexander, McCollum, and Paul, *J. Am. Chem. Soc.*, **72**, 4791 (1950).

(4) Wideqvist, *Arkiv Kemi, Mineral. Geol.*, **B 23**, No. 4 (1946); *Arkiv Kemi*, **2**, 321 (1950).

(5) Prout, *J. Am. Chem. Soc.*, **74**, 5915 (1952).

(6) Bush and Beauchamp, *J. Am. Chem. Soc.*, **75**, 2949 (1953); van Heyningen, *J. Am. Chem. Soc.*, **76**, 2241 (1954).

(7) Kohler and Heritage, *Am. Chem. J.*, **33**, 21 (1905) [*Chem. Zentr.*, I, 521 (1905)].

(8) Hauser, Yost and Ringler, *J. Org. Chem.*, **14**, 261 (1949).

(9) Kohler, *Am. Chem. J.*, **36**, 529 (1906) [*Chem. Zentr.*, I, 559 (1907)].

(10) Bergmann and Weiss, *Ann.*, **480**, 64 (1930).

(11) Kohler and Heritage, *Am. Chem. J.*, **33**, 153 (1905) [*Chem. Zentr.*, I, 824 (1905)].

(12) Keersblick, *Bull. soc. chim. Belg.*, **38**, 205 (1929) [*Chem. Zentr.*, II, 2036 (1929)].

(13) Hirao, *J. Pharm. Soc. Japan*, **73**, 1024 (1953) [*Chem. Abstr.*, **48**, 10724a (1954)].

(14) Blaise and Courtot, *Compt. rend.*, **140**, 370 (1905) [*Chem. Zentr.*, I, 726 (1905)]; cf. also ref. 9.

(15) Wotiz, Matthews, and Greenfield, *J. Am. Chem. Soc.*, **75**, 6342 (1953); cf. Wotiz and Matthews, *J. Am. Chem. Soc.*, **74**, 2559 (1952).