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The Use of Organolithium Compounds to Effect the Alkylation of 2- and 4-Picoline[1]

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The interaction of 2:2:1 molar ratio of 2-picoline, phenyllithium and alkyl halides and the same molar ratio of 4-picoline, methyllithium and alkyl halides gives high yields of the corresponding 2- and 4-picoline homologs. Comments are made concerning the course of these alkylations. The syntheses of 2,2'-dipyridylmethane and 2,2',2"-tripyridylmethane are described.

The alkali amide-effected alkylations of 2- and 4-picoline, which have been studied by Chichibabin and co-workers, have received much attention in recent years.[3] Although this method usually gives satisfactory yields of products, the required reaction times often are excessive.

Because of our favorable results[4–6] on the acylations of the lithium derivatives of 2-picoline and related tar bases, prepared from the tar bases and phenyllithium, we have extended our previous studies to alkylations. Although there are a few isolated examples recorded[7] in which phenyllithium has been used to effect the alkylation of 2-picoline, a detailed study of these reactions has apparently not been previously reported.

As a model synthesis, the preparation of 2-isobutylpyridine from 2-picoline, phenyllithium and isopropyl bromide was studied. These results are summarized in Table I. It may be seen that the use of a 1:1:1 molar ratio of these reagents and a reaction time of one-half hour to 18.5 hours gave 46.6–65.9% yields of 2-isobutylpyridine. However, when the molar ratio of the tar base anion to alkyl halide was increased to 2:1, the yield of product was increased to 92.5%.

Since Goldberg and Levine[8] have shown that 2-methyl-6-phenacylpyridine, prepared from 2,6-lutidine, phenyllithium and methyl benzoate, exists in the reaction mixture as its lithium derivative, a convenient explanation for the high yield of 2-isobutylpyridine obtained using a 2:1 molar ratio of tar base anion to alkyl halide would be to assume that the 2-isobutylpyridine exists as an anion as

$$\text{2-PyCH}_3 + \text{C}_6\text{H}_5\text{Li} \longrightarrow \text{2-PyCH}_2\text{Li (I)} + \text{C}_6\text{H}_6 \qquad (1)$$

$$\text{I} + \text{RX} \longrightarrow \text{2-PyCH}_2\text{R (II)} + \text{LiX} \qquad (2)$$

$$\text{I} + \text{II} \longrightarrow \text{2-PyCH}_3 + \text{2-PyCHRLi (III)} \qquad (3)$$

$$\text{2-PyCH}_3 = \text{2-picoline; RX} = i\text{-C}_3\text{H}_7\text{Br}$$

This scheme requires that step 3 go essentially to completion. This assumption is questionable since one would expect, on theoretical grounds, that the anion of 2-picoline is a weaker base than that of 2-isobutylpyridine. Furthermore, the addition of methyl benzoate to the reaction mixture gave 2-isobutylpyridine (II, 73.4%), 2-phenacylpyridine (2-$\text{PyCH}_2\text{COC}_6\text{H}_5$, 76.6%, which arises from I) and none of 2-$\text{PyCHRCOC}_6\text{H}_5$ (which could arise from III). Thus it appears that 2-isobutylpyridine probably does not exist as an anion in the reaction mixture.

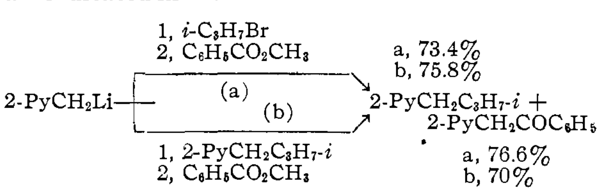
TABLE I

PHENYLLITHIUM-EFFECTED ISOPROPYLATION OF 2-PICOLINE

Run	Molar ratio of reactants[a]	Reaction time in hours[b]	2-Isobutylpyridine Yield, %
1	1:1:1	0.5	57.1
2	1:1:1	4.0	65.9
3	1:1:1	18.5	54.0
4	1:1:1	1.0[c]	46.6
5	1:1:2	1.0[c]	55.9
6	1:2:1	0.5	63.0
7	2:2:1	.5	92.5
8	1:1:2	.5	55.2

[a] Molar ratio of phenyllithium:2-picoline:isopropyl bromide. [b] This is the reflux time after the addition of the isopropyl bromide to the 2-picolyllithium is completed. [c] This reaction was effected by adding the 2-picolyllithium to an ether solution of isopropyl bromide; in the other runs the isopropyl bromide was added to the 2-picolyllithium.

Further evidence that 2-picolyllithium either cannot convert 2-isobutylpyridine to its anion or is more rapidly acylated by esters than is 2-isobutylpyridine was obtained by the interaction of these two reagents followed by the addition of methyl benzoate. From this experiment, 2-isobutylpyridine (II, 75.8%) and 2-phenacylpyridine (70%) were isolated.[9] The experiments described above are indicated in the scheme.



It is also unlikely that the high yield of 2-isobutylpyridine, obtained from two equivalents of 2-picolyllithium and one of isopropyl bromide, may be explained by the operation of a mass action effect since in runs 5 and 8 (Table I), which involve the interaction of two equivalents of the alkyl halide and one of 2-picolyllithium, considerably lower yields of 2-isobutylpyridine were obtained. A pos-

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[2] This paper is based on a portion of 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.

[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] N. N. Goldberg, L. B. Barkley and R. Levine, THIS JOURNAL, **73**, 4301 (1951).

[5] N. N. Goldberg and R. Levine, *ibid.*, **74**, 5217 (1952).

[6] N. N. Goldberg and R. Levine, *ibid.*, **77**, 3647 (1955).

[7] See, for example: (a) K. Ziegler and H. Zeiser, *Ann.*, **485**, 174 (1931); (b) O. Diels and K. Alder, *ibid.*, **505**, 103 (1933); (c) L. A. Walters and S. M. McElvain, THIS JOURNAL, **55**, 4625 (1933); (d) V. Prelog, L. Frankel and S. Szpilfogel, *Helv. Chim. Acta*, **29**, 484 (1946).

[8] N. N. Goldberg and R. Levine, THIS JOURNAL, **77**, 4926 (1955).

[9] In unpublished work from this Laboratory, it has been found that 2-isobutylpyridine may be acylated in high yields provided it is first converted to its anion by reaction with phenyllithium which is a stronger base than 2-picolyllithium.

TABLE II

THE PHENYLLITHIUM-EFFECTED ALKYLATIONS OF 2-PICOLINE AND 2-ETHYLPYRIDINE

Alkylating agent	Molar ratio of reactants[a]	Product, 2-C_5H_4NR R	Yield, %	B.p.		Picrate, m.p., °C.	
				°C.	Mm.	Obsd.	Literature
CH_3I	1:1:1	C_2H_5	40.8	148–149	746	110–111	107–108.3[b]
	2:2:1		73.2				
C_2H_5Br	1:1:1	n-C_3H_7	56.2	165–168	748	65–66.2[c]	64,[d] 68–69[e]
	2:2:1		92.3				74.6–75.1[b]
n-C_3H_7Br	2:2:1	n-C_4H_9	73.7	188–192	746	96.7–97.6	94[f]
i-C_3H_7Br	1:1:1	i-C_4H_9	57.1	97–102	55	97.0–97.6[g]	280–281[h]
	2:2:1		92.5				
n-C_4H_9	2:2:1	n-C_5H_{11}	78.8	102–107	25	72.0–72.8	73[i]
i-C_4H_9	2:2:1	i-C_5H_{11}	87.6	195–200	747	103.6–104.4	106[i]
$C_6H_5CH_2Cl$	2:2:1	$CH_2CH_2C_6H_5$	37.7	120–125	2	124–125.4	125.5–127[j]
		$CH(CH_2C_6H_5)_2$[k]	52.0	180–188	2	136.6–137	136.5–137.5[j]
CH_3I	1:1:1	i-C_3H_7[l]	62.5	154–156	726	117–118.5	118.1–118.7[b]
	2:2:1		38.9				
C_2H_5Br	2:2:1	sec-C_4H_9[l]	91.1	63–68	12	92.2–93	91.0[m]

[a] Ratio of phenyllithium : tar base : alkyl halide. [b] See reference 16. [c] *Anal.* Calcd. for $C_{14}H_{14}N_4O_7$: N, 16.00. Found: N, 15.86. [d] R. P. Mariella, L. F. A. Peterson and R. C. Ferris, THIS JOURNAL, **70**, 1494 (1948). [e] J. LeMen, *Bull. soc. chim. France*, 599 (1950). [f] G. J. Janz and R. Solomon, *Anal. Chem.*, **25**, 454 (1953). [g] *Anal.* Calcd. for $C_{15}H_{16}N_4O_7$: N, 15.38. Found: N, 15.53; the chloroplatinate melted at 192–194° (reference 5b and that in footnote *h* give 193°). [h] R. P. Mariella, THIS JOURNAL, **69**, 2670 (1947). [i] See reference 15a. [j] F. W. Bergstrom, T. R. Norton and R. A. Seibert, *J. Org. Chem.*, **10**, 452 (1945). [k] Apparently the methylene hydrogen atoms on the carbon atom directly attached to the pyridine ring in the initially formed 2-phenylethylpyridine are sufficiently acidic to be further alkylated. [l] 2-Ethylpyridine was alkylated; in all other cases 2-picoline was alkylated. [m] W. v. E. Doering and W. Z. Pasternak, THIS JOURNAL, **72**, 143 (1950).

sible explanation for the formation of the high yield of 2-isobutylpyridine might be that the actual alkylating agent is not the free alkyl halide but a quaternary complex formed by the reaction of the alkyl halide with the nitrogen atom of one equivalent of the picolyllithium. This complex might then alkylate the second equivalent of the 2-picolyllithium and regenerate one equivalent of this organometallic compound.[10]

2-Picoline was then alkylated with several other alkyl halides and the results are found in Table II. It can be seen that in those cases where both a 1:1 and a 2:1 molar ratio of 2-picolyllithium to alkyl halide were used, the latter ratio gives appreciably higher yields of products. The lithium derivative of 2-ethylpyridine was also alkylated and on methylation the yield of 2-isopropylpyridine which is obtained using a 2:1 molar ratio of reactants is considerably less (38.9%) than that (62.5%) which is obtained when a 1:1 molar ratio of reactants is used. This result is probably due to the difficulty encountered in separating the 2-isopropylpyridine from the large excess of 2-ethylpyridine which is present when the 2:1 ratio is employed.

In connection with the alkylation of 2-picoline, it was found that 2-picolyllithium may be heterylated[11] by reaction with 2-bromopyridine to give a mixture of 2,2′-dipyridylmethane (30.3%) and 2,2′,2″-tripyridylmethane (25.1%). 2,2′-Dipyridylmethane also was obtained by refluxing for 30 minutes a mixture of 2-picolyllithium and pyridine in the solvents indicated: ether (10.6%), toluene (20.9%), "xylol" (22.3%) and pyridine (36.8%).[12,13]

We next turned our attention to the alkylation of 4-picoline. Because of the fact that phenyllithium adds to the azomethine linkage of 4-methylquinoline[6] to give a mixture of 2-phenyl-4-methylquinoline (61–66%) and 2,2-diphenyl-4-methyl-1,2-dihydroquinoline (24–26%), we first *added 4-picoline to phenyllithium* in the absence of an alkylating agent. Azomethine addition occurred to a great extent since a mixture of 2-phenyl-4-methylpyridine (39%) and 2,6-diphenyl-4-methylpyridine (33%) was obtained. Therefore, apparently phenyllithium is not an effective reagent for the metalation of the methyl group of 4-picoline under the conditions employed.[14] However, when the phenyllithium was replaced by methyllithium as the condensing agent, it was found (Table III) that 4-picoline could be alkylated in good yields. Again the beneficial results which are obtained when a 2:2:1 molar ratio of tar base, organolithium compound and alkyl halide is used may be noted.

Finally, it should be pointed out that higher yields of alkylated products were obtained from 2- and 4-picoline using organolithium compounds as condensing agents than were obtained by Chichibabin[15] when he effected the same alkylations using sodium amide. Our results also compare quite favorably with the modified Chichibabin alkylations of

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(10) We wish to thank Dr. M. F. Dull for suggesting the possible formation of an intermediate complex. It is hoped to shed light on this point by a future kinetic study.

(11) In reference 3 (page 469) it is suggested that the term "heterylate" be used in a sense similar to that associated with alkylate and arylate, *i.e.*, to designate a process whereby a heterocyclic radical is introduced into an organic compound in place of a hydrogen atom.

(12) During the course of the present study, E. Leete and L. Marion [*Can. J. Chem.*, **30**, 563 (1952)] reported that they obtained 2,2,-dipyridylmethane in 36.7% yield by the reaction of 2 picolyllithium with pyridine in refluxing toluene for eight hours and only traces of this compound by the reaction of 2-picollythium with 2-bromopyridine.

(13) The methods described above represent an improvement over that reported by N. Sperber, D. Papa, E. Schwenk and M. Sherlock [THIS JOURNAL, **73**, 3856 (1951)] which gives the desired compound in 18% yield and involves the interaction of acetonitrile, 2-bromopyridine and sodium amide to give di-(2-pyridyl)-acetonitrile which is then hydrolyzed and decarboxylated.

(14) It should be pointed out that J. P. Wibaut and J. W. Hey [*Rec. trav. chim.*, **72**, 513 (1953)] indicate that they have prepared 4-alkylpyridines in yields of at least 60% of theory by *adding phenyllithium to 4-picoline* followed by the addition of alkyl halides. However, the only yield reported in their paper is that (60%) of 4-*n*-butylpyridine.

(15) A. E. Chichibabin: (a) *Bull. soc. chim. France*, [5] **3**, 1607 (1936); (b) [5] **5**, 429, 436 (1938).

TABLE III

THE METHYLLITHIUM-EFFECTED ALKYLATIONS OF 4-PICOLINE

Alkylating agent	Product, 4-C_5H_4NR R	Yield, %	B.p. °C.	Mm.	Picrate, m.p., °C. Obsd.	Liter.
C_2H_5Br	n-C_3H_7	74.0[a]	79–84	22	129.6–130.4	131[b]
n-C_3H_7Br	n-C_4H_9	40.8,[c] 68.1[a] 68.8,[e] 65.2[f]	98	20	111.5–112.4	112.8–113.8[b,d]
i-C_3H_7Br	i-C_4H_9	81.5[a]	93–95	23	120.0–120.4	122[g]
n-C_4H_2Br	n-C_5H_{11}	74.1[a]	115–120	21	104.6–105	102–103,[g] 104[d]
$C_6H_5CH_2Cl$	$CH_2CH_2C_6H_5$	43.1[a]	70.7–71.2[h]		163.4–164.1	162–163[i]
	$CH(CH_2C_6H_5)_2$	46.6[a]	176–181	1		
			74.6–75.6[j]		163.4–164.1[k]	

[a] The mixture of 4-picoline and methyllithium was refluxed for 30 minutes before adding the alkyl halide. [b] J. F. Arens and J. P. Wibaut, *Rec. trav. chim.*, 61, 59 (1942). [c] A 1:1:1 molar ratio of 4-picoline, methyllithium and alkyl halide was used; in all other cases a 2:2:1 molar ratio was used. [d] See reference 14. [e] Same as footnote *a* except reflux time was 2 hours. [f] Same as footnote *a* except reflux time was 4 hours. [g] See reference 15. [h] Melting point, recrystallized from 60–70° petroleum ether; see reference in footnote *j* of Table II. [i] B. Fels, *Ber.*, **37**, 2137 (1904). [j] Melting point, recrystallized from 30–60° petroleum ether. *Anal.* Calcd. for $C_{20}H_{19}N$: C, 87.87; H, 7.00. Found: C, 87.63; H, 6.57. [k] Recrystallized from 95% ethanol. *Anal.* Calcd. for $C_{26}H_{22}N_4O_7$: N, 11.15. Found: N, 11.43; a mixed melting point between this picrate and that of the monobenzylated derivative with the same melting point showed a sharp depression.

2- and 4-picoline recently described by Brown and Murphey.[16]

Experimental[17]

Synthesis of 2-Isobutylpyridine.—To 800 ml. of an ether solution of 2-picolyllithium (0.8 mole), prepared from 1.6 mole (11.2 g.) of lithium ribbon, 0.8 mole (125.6 g.) of bromobenzene and 0.8 mole (74.4 g.) of 2-picoline, there was added 0.4 mole (49.2 g.) of isopropyl bromide, dissolved in 50 ml. of anhydrous ether, over a 15–20 minute period. The reaction mixture was then refluxed for 30 minutes and poured onto 200–300 g. of crushed ice. The phases were separated and the aqueous layer was extracted with three 100-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and the solvent removed. The residue was distilled to give some unreacted starting materials and 50.5 g. (92.5%) of 2-isobutylpyridine, b.p. 97–102° at 55 mm.; picrate, m.p. 97–97.6°.

Reaction of 2-Picolyllithium, Isopropyl Bromide and Methyl Benzoate.—Isopropyl bromide (0.2 mole, 24.6 g.), dissolved in 30 ml. of anhydrous ether, was added to 0.4 mole of 2-picolyllithium and the reaction mixture was refluxed for 30 minutes. Then methyl benzoate (0.1 mole, 13.6 g.), dissolved in an equal volume of ether, was added and the reaction mixture was refluxed for an additional 30 minutes. On processing the reaction, as described above, there were obtained 19.8 g. (73.4%) of 2-isobutylpyridine, b.p. 97–102° at 55 mm., and 15.1 g. (76.6%) of 2-phenacylpyridine, b.p. 144–148° at 1.5 mm., m.p. 52.5–54°[4]; picrate, m.p. 181–182°.[4]

Reaction of 2-Picolyllithium, 2-Isobutylpyridine and Methyl Benzoate.—When 0.2 mole (27.0 g.) of 2-isobutylpyridine was added to 0.2 mole of 2-picolyllithium, followed, after a 30-minute reflux period, by 0.1 mole (13.6 g.) of methyl benzoate, there were obtained on processing 20.5 g. (75.8%) of recovered 2-isobutylpyridine, b.p. 97–101° at 55 mm., and 13.8 g. (70.0%) of phenacylpyridine, b.p. 142–148° at 1.5 mm., m.p. 52.5–54°.

Preparation of 2,2″-Dipyridylmethane. (a) **From 2-Picolyllithium and 2-Bromopyridine.**—A solution of 2-picolyllithium (0.4 mole) and 2-bromopyridine (0.2 mole, 31.6 g.) was refluxed for 30 minutes and processed in the regular manner to give 10.3 g. (30.3%) of 2,2′-dipyridylmethane, b.p. 126–132° at 5 mm. (lit. 102–106° at 0.5 mm.,[12] 106–110° at 0.5 mm.[13]), and 6.2 g. (25.1%) of 2,2′,2″-tripyridylmethane, m.p. 100–101° (from 60–70° petroleum ether). The dipyridyl derivative gave a yellow dipicrate, m.p. 202.5–203° dec. (from ethanol–acetic acid) (lit. 207.5–208°[12]). *Anal.* Calcd. for $C_{23}H_{16}N_8O_{14}$: C, 43.97; H, 2.57. Found: C, 44.03; H, 2.66. Analysis of 2,2′,2″-tripyridylmethane. Calcd. for $C_{16}H_{13}N_3$: C, 77.75; H, 5.30; N, 16.99. Found: C, 77.94; H, 5.23; N, 17.09. Attempts to obtain an analytically pure sample of a picrate of the tripyridyl derivative failed.

(b) **From 2-Picolyllithium and Excess Pyridine.**—Pyridine (200 ml.) was added to 0.2 mole of 2-picolyllithium in 200 ml. of ether. The ether was removed and the residue was refluxed for 17.5 hours and then processed to give 12.5 g. (36.8%) of 2,2′-dipyridylmethane, b.p. 126–132° at 5 mm.

Reaction of 4-Picoline with Phenyllithium.—A solution of 4-picoline (0.4 mole, 37.2 g.) and phenyllithium (0.4 mole) was refluxed for 30 minutes and processed to give 23.2 g. (39.2%) of 2-phenyl-4-methylpyridine, A (b.p. 113.5° at 1.8 mm.) and 16.4 g. (33.3%) of 2,6-diphenyl-4-methylpyridine, B (b.p. 189–190° at 1.4 mm.). Analysis of A: Calcd. for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.12; H, 6.70; N, 8.20. A gave a picrate, m.p. 187.6–188.3° (from 95% ethanol). *Anal.* Calcd. for $C_{18}H_{14}N_4O_7$: C, 54.27; H, 3.54; N, 14.07. Found: C, 54.37; H, 3.46; N, 14.09. A can be obtained as a solid, m.p. 48.4–49.7° (from 30–60° petroleum ether), on regeneration from its picrate. Analysis of B: Calcd. for $C_{18}H_{15}N$: N, 5.71. Found: N, 5.83.

Synthesis of 4-Isobutylpyridine.—4-Picoline (0.369 mole, 34.3 g.), dissolved in an equal volume of anhydrous ether, was added to methyllithium (0.369 mole in 400 ml. of ether), prepared in 92.4% yield from methyl iodide (0.4 mole, 56.8 g.) and lithium ribbon (0.8 mole, 5.6 g.), and the reaction mixture was refluxed for 30 minutes. Isopropyl bromide (0.185 mole, 22.7 g.), dissolved in an equal volume of ether, was added, the reaction mixture was refluxed for an additional 30 minutes and the mixture was processed to give 20.3 g. (81.5%) of 4-isobutylpyridine, b.p. 93–95° at 23 mm., picrate, m.p. 120–120.4°.

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[16] H. C. Brown and W. A. Murphey, THIS JOURNAL, **73**, 3308 (1951).

[17] The 2- and 4-picoline and 2-bromopyridine were kindly supplied by Dr. F. E. Cislak, Reilly Tar and Chemical Corp.