SYNTHESIS OF 4-ARYL-2-PICOLINES

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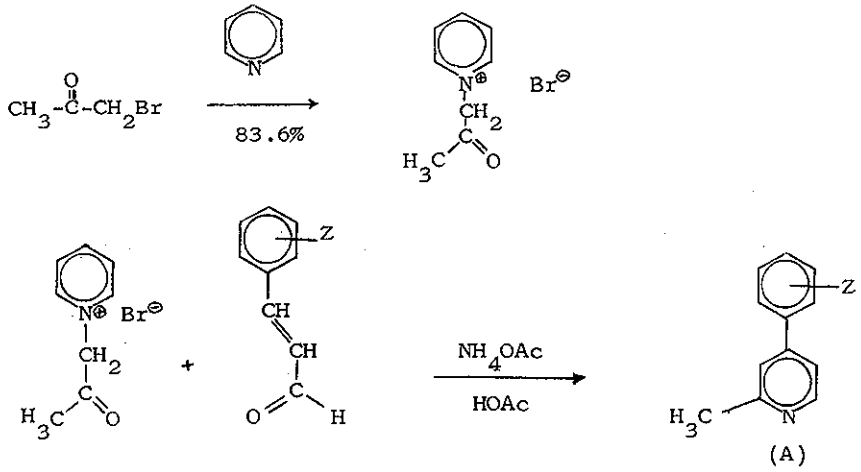
Thirteen 4-aryl-2-picolines were synthesized by the reaction of a pyridine ring formation in yields up to 42%. Six of the picolines synthesized were new compounds.

Thiosemicarbazone of 4-(m-aminophenyl)pyridine-2-carboxaldehyde (I) was reported to be the best antineoplastic agent of its series.[1] Although the compound was prepared by reduction of 4-(m-nitrophenyl)-2-picoline, the reaction of m-nitrobenzenediazonium chloride with 2-picoline was reported to afford the starting nitro-compound in poor yield (4%).[1] Subsequent improvement employed methylation of 4-phenylpyridine with methyllithium followed by nitration to afford 4-(m-nitrophenyl)-2-picoline in 17% yield.[2]

The present study was undertaken to prepare, by general pyridine ring formation,[3, 4] various 4-aryl-2-picolines which are needed to synthesize a variety of pyridinealdehydes of type I for biological evaluation.

The pyridinium salt (0.1 mole) obtained from bromoacetone and pyridine was allowed to react with substituted cinnamaldehydes[5,6] (0.1 mole) and ammonium acetate (1.3 mole) in acetic acid (100 ml) at 120° or at reflux (128°) for 5 hours. The reaction mixture was evaporated to about half of its original volume, diluted with 200 ml of water, and extracted with ether (5 x 100 ml). Usual workup gave a material which was purified by either recrystallization, chromatography on silica gel, or distillation in vaccum. Thirteen 4-aryl-2-picolines were thus obtained in yields up to 42% (Table I). Six of the picolines synthesized are new compounds. The NMR data of these picolines are collected in Table II.



Of thirteen substituted cinnamaldehydes prepared, m-methylcinnamaldehyde is a new compound obtained in 55% yield: bp 132-134° (9 mmHg); m/e, (M^+) 146; NMR, 2.25(s, 3H), 6.53(q, 1H), 7.06-7.56(m, 5H), 9.56 (d, 1H); semicarbazone mp 211.5-213° (satisfactory elemental analysis).

Table I Physical Data, Yields, and Picrates of 4-Aryl-2-picolines(A)

cpd	Z	% yield	mp °C (bp/mmHg) observed	literature	mass spectra (M^+)	mp of picrate[a]
1	H	26	(129-131/3)	(102-103/0.2)[2]	169	
2	o-NO_2	32	70.5-71	69-70[2]	214	
3	m-NO_2	37	156-157	155-156[1]	214	
4	p-NO_2	34.5	156.5-157.5	156-157[2]	214	
5	o-Br	22.5	(181/8)	new cpd	247	166-167.5(dec)
6	m-Br	17.6	(172-174/8)	new cpd	247	240-241(dec)
7	p-Br	42	74.5-76	75-76.2[7]	247	
8	o-Cl	34.3	(150-152/6)	new cpd	203	171-171.8(dec)
9	m-Cl	18.5	(158-159/8)	39-42[8]	203	
10	p-Cl	41.2	39-40 70.5-71.5	69-72[9]	203	
11	o-CH_3	18	(150-153/11)	new cpd	183	161.5-162(dec)
12	m-CH_3	15	(150/7)	new cpd	183	236.5-237(dec)
13	p-CH_3	17.7	(140-142/8)	new cpd	183	213-214(dec)

a. These picrates gave satisfactory elemental analysis.

Table II NMR Data of 4-Aryl-2-picolines(A)[a]

cpd	Z	pyridine ring Me(s, 3H)	phenyl ring Me(s, 3H)	other ring protons	pyridine ring H-6(dd, 1H)	$J_{5,6}$	$J_{3,6}$
1	H	2.59		7.26-7.73 (m, 7H)	8.63	5.2	1
2	o-NO_2	2.63		7.13-7.28 (m, 2H) 7.45-7.95 (m, 3H) 8.00-8.20 (m, 1H)	8.78	5	1
3	m-NO_2	2.70		7.43-8.67 (m, 6H)	8.76	5	1
4	p-NO_2	2.70		7.40-7.50 (m, 2H) 7.80-8.60 (q, 4H)	8.80	5	1
5	o-Br	2.57		7.00-7.33 (m, 5H) 7.65 (m, 1H)	8.54	5	1
6	m-Br	2.60		7.15-7.80 (m, 6H)	8.62	5	1
7	p-Br	2.53		7.13-7.70 (m, 6H)	8.53	5	1
8	o-Cl	2.62		7.15-7.60 (m, 6H)	8.65	5	1
9	m-Cl	2.63		7.27-7.73 (m, 6H)	8.73	5	1
10	p-Cl	2.56		7.21 (m, 2H) 7.47 (m, 4H)	8.53	5	1
11	o-CH_3	2.55	2.18	6.94-7.33 (m, 6H)	8.50	5	1
12	m-CH_3	2.57	2.41	7.15-7.44 (m, 6H)	8.50	5	1
13	p-CH_3	2.56	2.35	7.15-7.63 (m, 6H)	8.60	5	1

a. Recorded for $CDCl_3$ solution on a JBOL C-60-HL High Resolution NMR Instrument. The chemical shifts are in ppm downfield from internal TMS. J's are in Hz.

REFERENCES

1. K. C. Agrawal, A. J. Lin, B. A. Booth, J. R. Wheaton, and A. C. Sartorelli, J. Med. Chem., 17, 631 (1974).
2. K. C. Agrawal, B. A. Booth, S. M. DeNuzzo, and A. C. Sartorelli, J. Med. Chem., 18, 368 (1975).
3. W. Zecher and F. Krohnke, Chem. Ber., 94, 698 (1961).
4. F. Krohnke, Synthesis, 1 (1976).
5. G. Cignarella, E. Occelli, and E. Testa, J. Med. Chem., 8, 326 (1965).
6. R. E. Buckles and M. P. Bellis, Org. Syn., Coll. Vol. IV, 722 (1963).
7. L. F. Lin, S. J. Lee, and C. T. Chen, Institute of Chemistry, Academia Sinica, ROC, to be published.
8. C. T. Chen, S. F. Chen, and S. J. Lee, Bull. Inst. Chem., Academia Sinica, No. 24, 53 (1977).
9. P. Doyl and G. J. Stacey, Brit. 1147068 (Cl. c07d), 02 Apr 1969, Appl. 02 Dec 1966; Chem. Abstr., 71, 38813w (1969).

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