

SYNTHESIS OF 4-ARYL-2-PICOLINES

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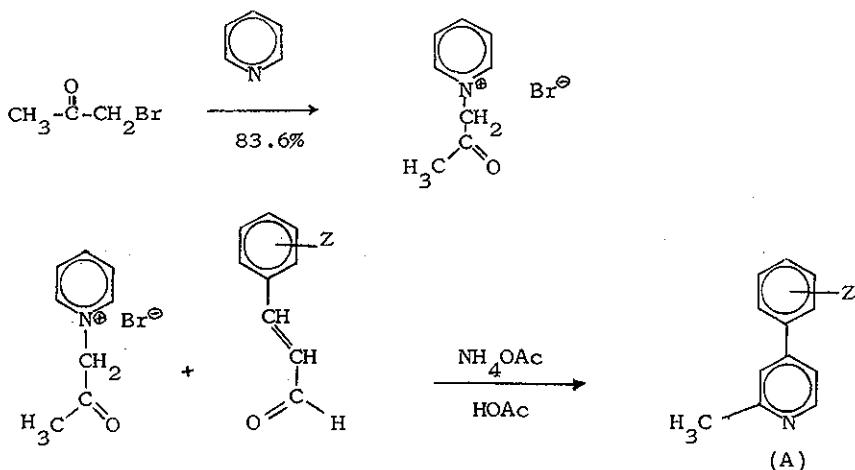
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Thirteen 4-aryl-2-picolines were synthesized by the reaction of a pyridine ring formation in yields up to 42%. Six of the picolines synthesized were new compounds.

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 vacuum. 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 observed	(bp/mmHg) 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) 39-40	39-42 ⁸	203	
10	p-Cl	41.2	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	phenyl ring	other ring	pyridine ring		
		Me(s, 3H)	Me(s, 3H)	protons	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 CDCl₃ solution on a JEOL C-60-HL High Resolution NMR Instrument. The chemical shifts are in ppm downfield from internal TMS. J's are in Hz.

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