3-Lithiated Pyridines and their Reactions with Electrophiles

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The direct metallation of a pyridine ring CH has seldom[1,2] been achieved: organolithium reagents normally add across the C=N bond[3]. 3-Lithiation of certain polychloropyridines with butyllithium was the first exception[1] and recently Meyers and Gabel[2] lithiated a 4-(2-oxazolinyl)-pyridine in the 3-position and studied further reactions with various electrophiles. In the benzenoid series, *ortho*-metallation is well known, e.g. of benzyldimethylamine[4] and *N*-methylbenzamide[5,6].

We now report that 2-aminocarbonylpyridines also readily undergo lithiation at the 3-position. Benzyl 2-picolinamide (**1**) was prepared by the phosphoroazo method[7] in quantitative yield (contrast previously reported procedures[8,9]). Excess butyllithium in tetrahydrofuran at −78 °C gave the bis (*N*- and *ortho*-) lithiated product (**3**). Subsequent condensation with benzoyl, 4-chlorobenzoyl, and 4-methylbenzoyl chlorides yielded initially the simple 3-acylated derivatives (**5a, b, c**; 80, 82, and 89%, respectively). However, these 2,3-disubstituted pyridines (**5a, b, c**) cyclised spontaneously to form stable bicyclic systems (**7a, b, c**); although the uncyclised product **5c** derived from 4-methylbenzoyl chloride was isolated with difficulty, it gave **7c** on attempted crystallisation. This cyclisation is expected: γ-hydroxyamides cyclodehydrate or cyclodeaminate to form γ-lactams or γ-lactones with acids[10].

The structures of the bicycles **7a, b, c** were supported by analyses, and by their I.R. ($\nu_{O-H}=3200\ cm^{-1}$, $\nu_{C=O}=1710\ cm^{-1}$), N.M.R., and mass spectra. Condensation of **3** with 4-methylbenzaldehyde gave the corresponding hydroxyamide **9c**. Similarly, a reaction of **3** with benzophenone gave the carbinol **11**. 2-Methylaminocarbonylpyridine (**2**; prepared from ester[11]) similarly underwent lithiation at the 3-position. Subsequent reaction with the appropriate acid chlorides yielded bicyclic products **8a** and **8c**, whereas the corresponding benzaldehydes formed the hydroxyamides **10c** and **10d**. We also carried out a reaction with benzophenone which gave the expected product **12**.

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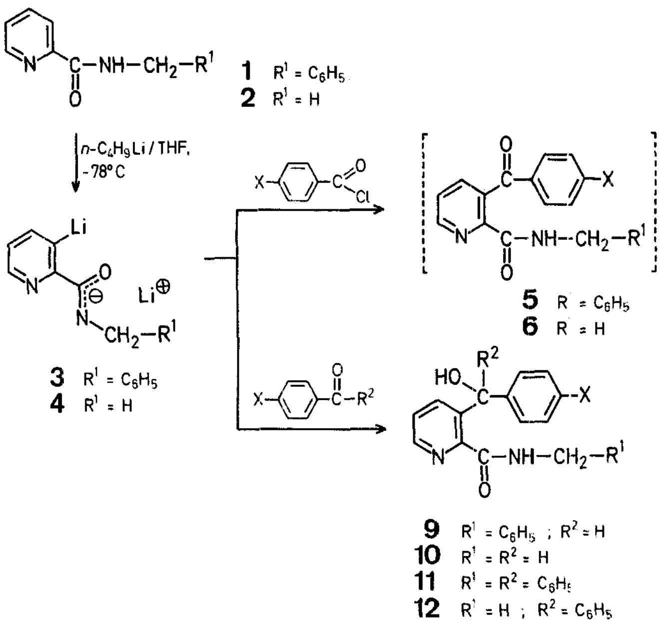

These results indicate a convenient method for the metalation of the 3-position of pyridine and for the preparation of 2,3-disubstituted pyridines.

3-Substituted N-Benzyl- and N-Methylpyridine-2-carboxamides (5, 7-12); General Procedure:

N-Benzylpyridine-2-carboxamide (1; 100 mg, 0.47 mmol) (or an equivalent amount of the N-methyl analogue) in tetrahydrofuran (2 ml) is added with stirring to butyllithium (0.94 mmol) in hexane and dry tetrahydrofuran (5 ml) at −78 °C under nitrogen. The mixture is stirred for 15 min at −78 °C; then, the acyl halide (0.94 mmol) or the aldehyde or ketone (0.94 mmol) in tetrahydrofuran (2 ml) is added to the dark blue (benzyl) or yellow (methyl) solution. Stirring is continued for 1 h at −78 °C and for 1 h at 20 °C before water (2 ml) is added and the solvent removed at 100 °C/50 torr. The residue is taken up in chloroform, washed with water, dried with magnesium sulfate, and evaporated at 20 °C/20 torr. The crude product is purified by crystallisation or preparative T.L.C. [silica gel, petroleum ether (b.p. 40–60 °C), ethyl acetate] to give the desired product.

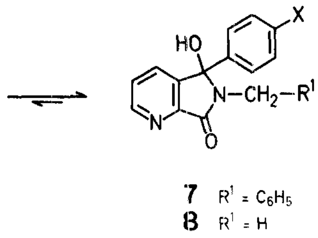

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Table. 2,3-Disubstituted Pyridines (5, 9-12) and 5,6-Disubstituted 5-Hydroxy-7-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridines (7, 8) prepared

Starting material	Reagent	Product[a]	Yield [%]	m.p. [°C] (solvent)	Crystal form	Molecular formula[b]
1	4-H_3C—C_6H_4—COCl	5c	89	oil		$C_{21}H_{18}N_2O_2$ (330.4)
		7c[c]	89	155–157° (ethyl acetate/ pet. ether b.p. 40–60°)	needles	$C_{21}H_{18}N_2O_2$ (330.4)
1	C_6H_5—COCl	7a	80	154–155° (ethyl acetate/ pet. ether b.p. 40–60°)	colourless plates	$C_{20}H_{16}N_2O_2$ (316.4)
1	4-Cl—C_6H_4—COCl	7b	82	219–221° (ethyl acetate/ pet. ether b.p. 40–60°)	yellowish prisms	$C_{20}H_{15}ClN_2O_2$ (350.8)
1	4-H_3C—C_6H_4—CHO	9c	64	oil		$C_{21}H_{20}N_2O_2$ (332.4)
1	$(C_6H_5)_2C$=O	11	72	165–167° (95% ethanol)	white flakes	$C_{26}H_{22}N_2O_2$ (394.5)
2	C_6H_5—COCl	8a	56	214–216° (ethyl acetate/ pet. ether b.p. 40–60°)	micro-crystals	$C_{14}H_{12}N_2O_2$ (240.3)
2	4-H_3C—C_6H_4—COCl	8c	49	188–191° (ethyl acetate/ pet. ether b.p. 40–60°)	micro-crystals	$C_{15}H_{14}N_2O_2$ (254.3)
2	4-H_3C—C_6H_4—CHO	10c	58	115–117° (95% ethanol)	prisms	$C_{15}H_{16}N_2O_2$ (256.3)
2	4-H_3CO—C_6H_4—CHO	10d	61	112–114° (95% ethanol)	fine needles	$C_{15}H_{16}N_2O_3$ (272.3)
2	$(C_6H_5)_2C$=O	12	66	168–171° (95% ethanol)	prisms	$C_{20}H_{18}N_2O_2$ (318.4)

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[a] All compounds were characterised by I.R. and ^{1}H-N.M.R. spectrometry and for 7a, b, c by M. S. spectrometry.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.40; H, ±0.30; N, ±0.30.

[c] Conversion 1→5c→7c without isolation of 5c (heating in ethyl acetate).

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