

Synthesis of Imidazolopyridine Derivatives by an Unusual
Reaction of N-Benzylpicolinamides with Phosphorus Pentachloride

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Reaction of N-benzylpicolinamides (1) with phosphorus pentachloride in the presence of pyridine gave rise to 3-phenyl-imidazolo[3,4-a]pyridines (2). Based on the reaction with N-benzyl-d₇-picolinamide, a possible mechanism for the formation of 2 is proposed.

During the course of our studies on the preparation of imidoxy chlorides of compounds possessing a pyridine ring, we came across an unusual reaction between N-benzylpicolinamide and phosphorus pentachloride in pyridine.

N-Benzylpicolinamide (1a)¹, prepared by the reaction of ethyl picolinate with benzylamine, was added to the mixture of pyridine, phosphorus pentachloride and phosphorus oxychloride. The reaction mixture was heated at 50° for 4 h. The residue which was obtained after the removal of the excess phosphorus oxychloride was chromatographed on silica gel to give 3-phenylimidazolo[3,4-a]pyridine (2a) in a 26% yield as colorless needles, mp 107-109°. Anal. Calcd. for C₁₃H₁₀N₂: C, 80.48; H, 5.19; N, 14.42. Found: C, 80.65; H, 5.37; N, 14.48. uv λ_{max} (cyclohexane) : 209 (26,000), 231.4 (19,4000), 318.3 (13,600)². nmr δ (CDCl₃): 6.50 (1H, dd, J=7 Hz, J=6.5 Hz), 6.67 (1H, dd, J=6.5 Hz, J=9 Hz), 7.35-7.80 (5H, m), 7.43 (1H, d, J=9 Hz), 7.53 (1H, s), 8.21 (1H, d, J=7 Hz).

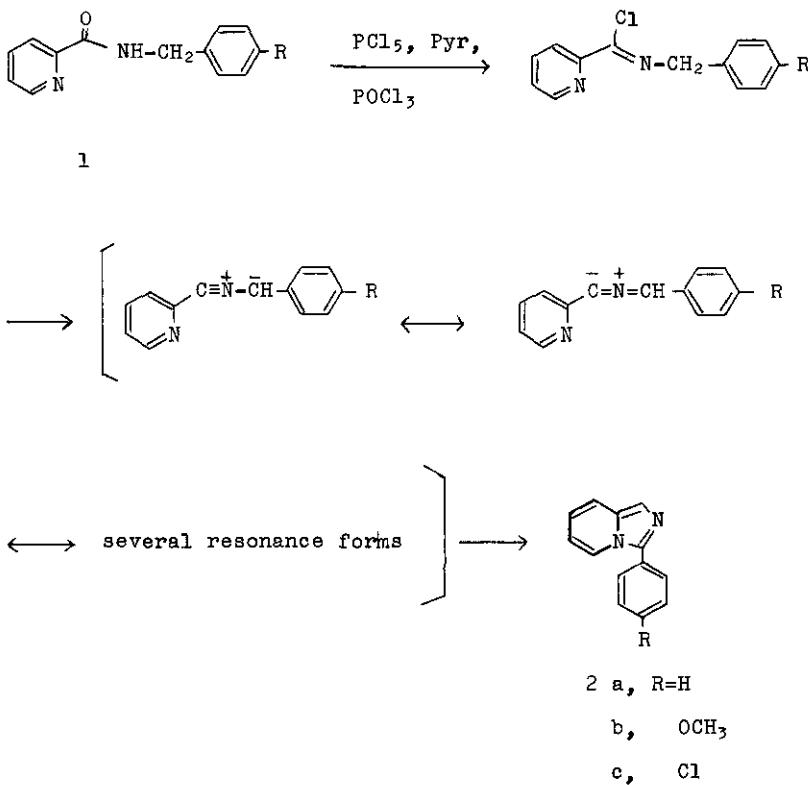
The structure of 2a was unambiguously confirmed by comparison with an authentic sample³ prepared from 2-benzamidomethylpyridine (3) and phosphorus oxychloride.

In the similar manner, p-methoxy- and p-chloro-substituted compounds (2b and 2c) were prepared in 18 and 31% yield, respectively.

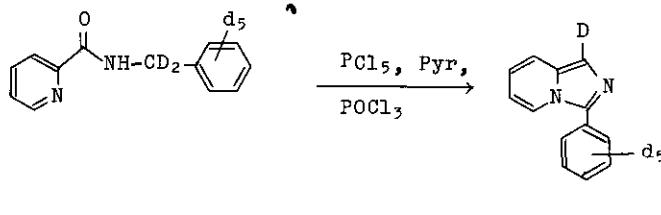
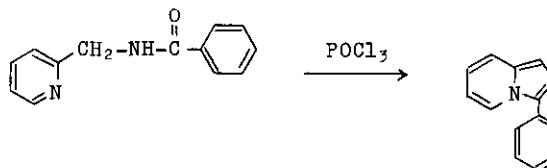
3-(p-methoxyphenyl)imidazolo[3,4-a]pyridine (2b): mp 85-87°. Anal. Calcd. for C₁₄H₁₂N₂O: C, 74.99; H, 5.38; N, 12.49. Found: C, 75.13; H, 5.38; N, 12.53. nmr δ (CDCl₃): 3.87 (3H, s), 6.51 (1H, dd, J=7 Hz, J=6 Hz), 6.71 (1H, dd, J=6 Hz, J=9 Hz), 7.15 (2H, d, J=9 Hz), 7.51 (1H, d, J=9 Hz), 7.58 (1H, s), 7.78 (2H, d, J=

9 Hz), 8.23 (1H, d, J=7 Hz).

3-(p-chlorophenyl)imidazolo[3,4-a]pyridine (2c): mp 103-105°. Anal. Calcd. for $C_{13}H_9N_2Cl$: C, 68.27; H, 3.96; N, 12.25; Cl, 15.50. Found: C, 68.49; H, 4.02; N, 12.04; Cl, 15.26. nmr δ (CDCl₃): 6.62 (1H, dd, J=7 Hz, J=6 Hz), 6.82 (1H, dd, J=6 Hz, J=9 Hz), 7.54 (1H, d, J=9 Hz), 7.60 (2H, d, J=8 Hz), 7.65 (1H, s), 7.85 (2H, d, J=8 Hz), 8.31 (1H, d, J=7 Hz).



In order to investigate the reaction mechanism, N-benzyl-d₇-picolinamide (4) which was prepared from picolinamide and benzyl-d₇-chloride in the presence of sodium hydride was treated with phosphorus pentachloride in phosphorus oxychloride containing an equimolar amount of pyridine. The reaction mixture was heated at 50° for 4 h. The residue remaining after the removal of the phosphorus oxychloride was chromatographed on silica gel to give 1-deutero-3-phenyl-d₅-imidazolo[3,4-a]-pyridine (5), mp 109-110°, in 21% yield. nmr δ (CDCl₃): 6.56 (1H, dd, J=6 Hz, J=7 Hz), 6.74 (1H, dd, J=6 Hz, J=9 Hz), 7.43 (1H, d, J=9 Hz), 8.33 (1H, d, J=7 Hz). As you can see, a singlet around 7.5 ppm due to the proton of the C-1 position of



5 disappeared in the nmr. Mass spectrum: m/e 200 (M^+). From the nmr and mass spectra, it is clear that the C-1 position of 5 was deuterated. Consequently, it is reasonable to consider that 5 might be formed via intramolecular cyclization of one of the equilibrium mixture of the initially formed nitril-ylide, and 1,3-deuterium shift occurred at some stage of the equilibration of the initially formed nitril-ylide.

REFERENCES

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