

S_{RN}1 REACTION. SYNTHETIC APPLICATION TO 4-AZAINDOLES

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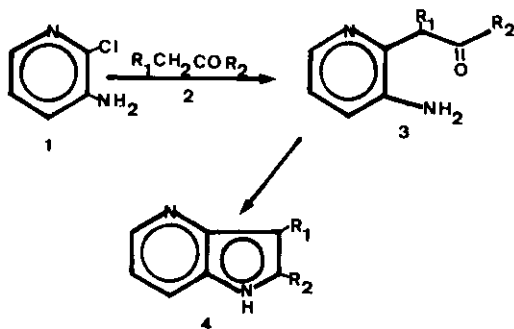
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Abstract.— A new synthetic method for 4-azaindoles, based on nucleophilic heteroaromatic substitution via a radical intermediate (S_{RN}1 reaction) is described.

The chemistry and potential biological activity of azaindoles is an area of current interest but the compounds remain relatively inaccessible¹. Concerning to 4-azaindoles (1H-pyrrolo [3,2-b]pyridine) few synthetic methods are described. The limitations of most of them are a) lack of reproducibility of results due to the drastic conditions of work (case of base-catalyzed cyclisations of 3-acylaminopicolines²); b) lengthy and unconvencionality of the synthetic method (case of photochemical ring contraction of naphthyridines³); c) dependence upon the availability of suitable substituted pyridines (case of ring closures of pyridylhydrazones⁴ or 3-nitropicolines⁵). All these reasons justify the investigation of new methods.

We wish to report here a simple good-yield method based on nucleophilic heteroaromatic substitution via a radical intermediate (S_{RN}1 reaction⁶) derived from 3-amino-2-chloropyridine (1).

Photostimulated reactions of (1) with the appropriate potassium enolate of (2) in liquid ammonia at -33°C, proceeded smoothly to afford (4) through the intermediate (3). The results are reported in the Table.



	R ₁	R ₂
a	H	H
b	H	CH ₃
c	CH ₃	H
d	(CH ₂) ₄	
e	CH ₃	Ph
f	H	Pyr

In a typical experiment, 0.01 mole of 3-amino-2-chloropyridine was added to the potassium enolates of (2), prepared by addition of 0.02 mole of the carbonyl compound (2), dissolved in 5 ml of anhydrous ether, to 0.02 mole of potassium *t*-butoxide in 400 ml of liquid ammonia, under nitrogen. After irradiation for 100 minutes, with a high pressure mercury lamp (Philips HPK 125W), the mixture was quen-

ched with ammonium chloride. The ammonia was evaporated and the residue was extracted with methylene chloride. The product (4) was isolated by column chromatography (alumina I) eluting with methylene chloride-ethyl acetate. Recrystallization from methanol or benzene gave the pure 4-azaindoles: 1H-pyrrolo [3,2-b] pyridine (4-azaindole) (4a), 2-methyl-1H-pyrrolo [3,2-b] pyridine (4b), 3-methyl-1H-pyrrolo [3,2-b] pyridine (4c), 6,7,8,9-tetrahydro-5H-pyrrolo [3,2-b] indole (4d), 2-phenyl-3-methyl-1H-pyrrolo [3,2-b] pyridine (4e), 2-(2-pyridyl)-1H-pyrrolo [3,2-b] pyridine (4f). See Table.

Table

Pro- ^a duct	Yield ^b %	M.p. °C	¹ H-NMR (CD ₃ OD/TMS) ^c ppm
4a	62	121-2 ⁵	6.67(d, 1H, C ₃ -H), 7.08(dd, 1H, C ₆ -H), 7.45(d, 1H, C ₂ -H), 7.64(dd, 1H, C ₇ -H), 8.39(dd, 1H, C ₅ -H) ⁷ .
4b	54	192-3 ²	2.47(s, 3H, CH ₃), 6.27(s, 1H, C ₃ -H), 6.97(dd, 1H, C ₆ -H), 7.62(dd, 1H, C ₇ -H), 8.12(dd, 1H, C ₅ -H) ⁸ .
4c	59	227-8 ⁹	2.35(s, 3H, CH ₃), 7.05(dd, 1H, C ₆ -H), 7.12(d, 1H, C ₂ -H), 7.73(dd, 1H, C ₇ -H), 8.20(dd, 1H, C ₅ -H) ¹⁰ .
4d	52	260-2 ¹¹	1.9(m, 4H, CH ₂), 2.8(m, 4H, CH ₂), 6.90(dd, 1H, C ₃ -H), 7.44(dd, 1H, C ₄ -H), 8.28(dd, 1H, C ₂ -H) ¹² .
4e	30	238-9	2.51(s, 3H, CH ₃), 7.04(dd, 1H, C ₇ -H), 7.3-7.7(m, 6H), 8.24(dd, 1H, C ₅ -H).
4f	21	251-2	7.0-7.9(m, 6H), 8.3(dd, 1H, C ₇ -H), 8.57(m, 1H, C ₆ -H pyridinic).

^aThe microanalyses were in good agreement with the calculated values (C±0.22, H±0.19 N±0.10).

^bYields of purified compounds are given. ^cRecorded at 60 MHz on a Perkin-Elmer R-12B spectrometer.

REFERENCES and NOTES

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8. J_{5,6} = 8.0, J_{6,7} = 4.8, J_{5,7} = 1.3, J_{3,CH₂} = 0.8.
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