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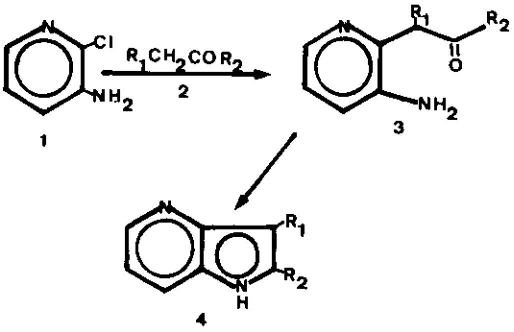
$S_{RN}1$ REACTION.SYNTHETIC APPLICATION TO 4-AZAINDOLES

Rafael Fontan,Carmen Galvez[•] and Pere Viladoms
Departamento de Quimica Orgánica,Facultad de Química de la Universidad
de Barcelona,Spain

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 inaccessible[1].
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-acylaminopicolines[2]);b) lengthy and unconventionality of the synthetic method (case of photochemical ring contraction of naphthyridines[3]);c) dependence upon the availability of suitable substituted pyridines (case of ring closures of pyridylhydrazones[4] or 3-nitropicolines[5]). 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 ($S_{RN}1$ reaction[6]) derived from 3-amino-2-chloropyridine (1).
Photostimulated reactions of (1) with the appropiate potassium enolate of (2) in liquid ammonia at -33ºC,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 quenched 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: 1*H*-pyrrolo [3,2-b] pyridine (4-azaindole) (*4a*), 2-methyl-1*H*-pyrrolo [3,2-b] pyridine (*4b*), 3-methyl-1*H*-pyrrolo-[3,2-b] pyridine (*4c*), 6,7,8,9-tetrahydro-5*H*-pyrido [3,2-b] indole (*4d*), 2-phenyl-3-methyl-1*H*-pyrrolo [3,2-b] pyridine (*4e*), 2-(2'-pyridyl)-1*H*-pyrrolo [3,2-b] pyridine (*4f*). See Table.

Table

Product[a]	Yield[b] %	M.p. ºC	^{1}H-NMR (CD_3OD/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	200-2[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).

[a] The microanalyses were in good agreement with the calculated values (C±0.22,H±0.19 N±0.10).

[b] Yields of purified compounds are given. [c] Recorded at 60 MHz on a Perkin-Elmer R-12B spectrometer.

REFERENCES and NOTES

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7. $J_{2,3}$= 3.3, $J_{5,6}$= 8.3, $J_{6,7}$= 4.7, $J_{5,7}$= 1.3.
8. $J_{5,6}$= 8.0, $J_{6,7}$= 4.8, $J_{5,7}$= 1.3, J_{3,CH_3} = 0.8.
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10. $J_{5,6}$= 8.0, $J_{6,7}$= 4.9, $J_{5,7}$= 1.3, J_{2,CH_3} = 0.8.
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12. $J_{2,3}$= 8.0, $J_{3,4}$= 4.7, $J_{2,4}$= 1.3.

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