Pergamon

Tetrahedron Letters, Vol. 35, No. 13, pp. 1995-1998, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0193-2

Synthesis and Reactivity of 1-Substituted-3*H*-Pyrrolo[2,3-*b*] Pyridin-3-one

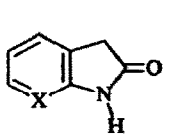
E. Desarbre and J.Y. Mérour*

Laboratoire de Chimie Bioorganique et Analytique, associé au C.N.R.S., Université d'Orléans,
BP 6759, 45067 Orléans Cedex 2, France.

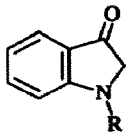
Abstract: *1-Substituted-pyrrolo[2,3-b]pyridin-3-ones (7-azaindolinones) have been obtained by Baeyer-Villiger oxidation. Reaction of 7-azaindolinone with aromatic aldehydes led to 2-substituted-7-azaindolinones. Synthesis of pyrido[3',2':4,5]pyrrolo[3,2-b]naphtyridine have been described.*

Oxoindole derivatives, like oxindoles **1**, possess various biological properties[1,2] and indolinones **3**[3,4] are good intermediates for indolic compounds synthesis. The primary interest in pyrrolopyridines (azaindoles), in particular 1*H*-pyrrolo[2,3-*b*]pyridines (7-azaindoles), is their analogous framework with indole derivatives[5]. 1*H*-Pyrrolo[2,3-*b*] pyridines have been drawing much attention in biochemical and physicochemical studies like as non-invasive optical probes of protein structure[5b], as effective inhibitors of HIV reverse transcriptase[5c] or as a part of the gargantuan research effort on serotoninergic neurotransmission[5d].

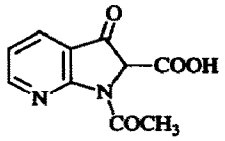
In contrast with 7-azaoxindole[6] **2**, the synthesis of 7-azaindolinones **6** has not been described. Willette has reported the preparation of (1-acetyl-3-oxo-pyrrolo[2,3-*b*]pyridin-2-yl) carboxylic acid **4**[7], which can be a precursor of azaindolinone **6** but, in agreement with the results of Parrick[8], we were unable to repeat Willette's work. The standard preparations of indolinones **3**[1,9], despite numerous attempts, met with failure when applied to the synthesis of 7-azaindolinones **6**.



1 X = CH
2 X = N



3

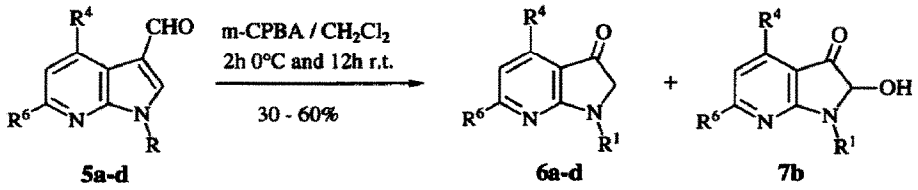


4

In this paper, we report the preparation of 1-substituted-3*H*-pyrrolo[2,3-*b*]pyridin-3-ones or 7-azaindolinones **6a-d** by Baeyer-Villiger oxidation of 3-carboxaldehyde-1*H*-pyrolo[2,3-*b*]pyridine (3-formyl-7-azaindole) **5a-d**. As described in a recent paper[10] on a new synthesis of indolinones **3**, the formyl compounds **5a-d**, obtained by reaction of hexamethylenetetramine[11] with the corresponding 7-azaindole,

were treated with 1.3 eq *meta*-chloroperbenzoic acid (*m*-CPBA) at 0°C during 2h then at room temperature during 12h in CH_2Cl_2 to give 7-azaindolinones **6a-d** after silica gel chromatography (scheme 1).

Scheme 1

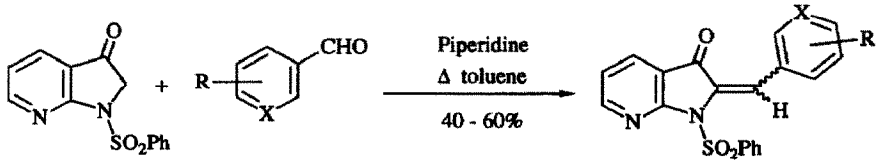


5a-d **6a-d** **7b**

				Isolated yield (%)		
	R_1	R_4	R_6	**5**	**6**	**7**
a	$COCH_3$	H	H	10	30	-
b	SO_2Ph	H	H	10 - 15	40	15 - 10
c	SO_2Ph	Cl	H	-	60	-
d	SO_2Ph	H	Cl	-	52	-

As precedently described for indolinones **3**[10], overoxidation of compound **6b** was observed to give α-hydroxyketone **7b**. This different behaviour of **5a** and **5b** towards oxidation corroborates our findings[10] on the important role played by the protecting group on the 1-position. In each case, formation of pyridinium N-oxide was not observed during the oxidation step. The formyl group in 3-position was probably more reactive than the nitrogen in the pyridine ring; this selectivity has also been observed in the ellipticine series[12].

Scheme 2



6b **8e-h** **9e-h**

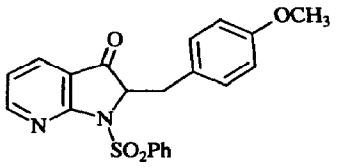
8	R	X	Isolated yield of **9**
e	4-OCH_3	CH	45% (Z+E)
f	4-Cl	CH	43% (Z+E)
g	2-NO_2	CH	40% (E), 20% (Z+E)
h	H	N	45% (Z+E)

Azaindolinones **6** can be substituted in 2-position through an aldol condensation sequence.

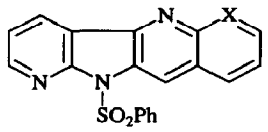
Thus, treatment of ketone **6b** with aromatic aldehydes **8e-h** in refluxing toluene with one drop of piperidine gave directly the corresponding α,β-unsaturated ketones **9e-h** as a mixture of Z and E isomers in the approximate ratio 1 / 1 (the proportion was determined by ^{1}H-NMR) (Scheme 2). Steric hindrance between the nitro and phenyl sulfonyl groups favoured the synthesis of compound (E) **9g** rather than of compound (Z) **9g**.

Reduction of compound **9e** by hydrogen over palladium led to compound **10e** in a 60% yield and gave access to 2-substituted azaindolinones which can also lead to azatryptamines substituted in the 2-position as in the indole series[4].

The use of 2-nitrobenzaldehyde in the aldolisation reaction led to compound **9g**. After hydrogenation of the nitro group over Pd/C and intramolecular cyclisation in the mixture, the **9g** (E) stereomer gave the tetracyclic compound **11i** in 51% yield. This two-step procedure can be reduced to a more straighforward synthesis by direct treatment of **6b** with 2-amino-3-formylpyridine[13] in toluene to give compound **11j** in 55 % yield. Compounds **11** are analogs of the azaellipticine series[14] and we are currently investigating the synthetic potential of 7-azaindolinones **6**.



10e



11i X = CH
11j X = N

Typical procedure: To a solution of 3-formyl-1-phenylsulfonyl-pyrrolo[2,3-*b*]pyridine (4 mmol) in CH_2Cl_2 (30 mL), *m*-CPBA (5.2 mmol) was added at 0°C. After 2h at 0°C, the mixture was stirred at room temperature overnight. A solution of Na_2SO_3 10% (40mL) was added and decanted, the aqueous solution was extracted with CH_2Cl_2 (2 X 30 mL). Organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed over silica gel using EP / AcOEt (7 : 3, v : v) as eluent to give **6b** (40%).

Acknowledgments: We thank Dr Faure for the ^{13}C-NMR spectra data.

REFERENCES AND NOTES:

1. Sundberg, R.J. *The Chemistry of Indoles*; Academic Press: New York. 1970.
2. Wiseman, E.W.; Chaini, J.; Mac Manus, J.M. *J. Med. Chem.* **1973**, *16*, 131-134.
3. Buzas, A.; Herisson, C.; Lavielle, C. *Synthesis* **1972**, 129-130.
4. Buzas, A.; Mérour, J. Y. *Synthesis* **1989**, 458-461.
5. (a) Yakhontov, L.N.; Prokopov, A.A. *Russ. Chem. Rev.* **1980**, *49*, 428-444.
   (b) Chen, Y.; Gai, F.; Petrich, J.W. *J. Amer. Chem. Soc.* **1993**, *115*, 10158-10166.
   (c) Seela, F.; Gumbioswki, R. *Helv. Chim. Acta* **1991**, *74*, 1048-1058.
   (d) Macor, J.E.; Post, R.; Ryan, K.; *J. Heterocyclic Chem.* **1992**, *29*, 1465-1467.

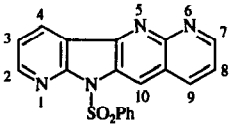
6. (a) Marfat, A.; Carta, M.P. *Tetrahedron Lett.* **1987**, *28*, 4027-4030.
(b) Valentine, J.J.; Nakunishi, S.; Hageman, D.L.; Snider, R.M.; Spencer, R.W.; Vinick, F.T. *Biorg. Med. Chem. Lett.* **1992**, *2*, 333-338.
7. Willette, R.E. *J. Chem. Soc.* **1965**, 5874-5876.
8. Parrick, J.; Wilcox, R.; Kelly, A.H. *J. Chem. Soc., Perkin Trans. I* **1980**, 132-135.
9. (a) Raileanu, D.; Contantinescu-Simon, O.; Mosanu, E.; Nenitzescu, C. D. *Rev. Roum. Chim.* **1967**, *12*, 105-108; *Chem. Abstr.* **1968**, *68*, 21775a.
(b) Hampel, W. *J. Prakt.Chem.* **1969**, *311*, 78-81.
(c) Nimtz, M.; Hefelinger, G. *Liebigs Ann. Chem.* **1987**, 765-770.
(d) Etienne, A. *Bull. Soc. Chim. Fr.* **1948**, 651-658.
10. Bourlot, A.S.; Desarbre, E.; Mérour, J.Y. *Synthesis*, in press.
11. Verbiscar, A.J. *J. Med. Chem.* **1972**, *15*, 149-152.
12. Plug, J.P.M.; Koonen, G.J.; Prandit, U.K. *Synthesis* **1992**, 1221-1222.
13. Turner, J.A. *J. Org. Chem.* **1983**, *48*, 3401-3412.
14. (a) Rivalle, C.; Ducrocq, C.; Lhoste, J.M.; Wendling, F.; Bisagni, E. *Tetrahedron* **1981**, *37*, 2097-2103.
(b) Praly-Deprez, I.; Rivalle, C.; Belehradek, J.; Huel, C.; Bisagni, E. *J. Chem. Soc. Perkin Trans. I* **1991**, 3173-3175.
(c) Estel, L.; Linard, F.; Marsais, F.; Godard, A.; Quéguiner, G. *J. Heterocyclic Chem.* **1989**, *26*, 105-112.

15. Identification of compounds **6b**, **11i**, and **11j**.

6b: m.p: 172 - 174°C; I.R. (KBr) υ = 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm: 4.39 (s, 2H, H_2); 7,10 (dd, 1H, H_5, J = 7.3 Hz, J = 5.1 Hz); 7.50 -7.70 (m, 3H); 7.95 (dd, 1H, H_4, J = 7.3 Hz, J = 1,5 Hz); 8,15 (d, 2H, H_{arom}, J = 8.1 Hz); 8.63 (dd, 1H, H_6, J = 5.1 Hz, J = 1.5 Hz); ^{13}C-NMR (DMSO-d_6, 100 MHz) 56.76 (C_2), 117.76 (C_{4a}), 119.42 (C_5), 127.89 ($C_{2'}$), 129.33 ($C_{3'}$), 133.58 (C_4), 134.12 ($C_{4'}$), 138.23 ($C_{1'}$), 155.98 (C_6), 162.99 (C_{7a}), 192.65 (C_3) ; M. S. (C.I., NH_3): m/z 275 (M^++1).

11i: m.p:.242 - 244°C; I.R. (KBr) υ = 1190 cm^{-1} (SO_2); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm: 7.35 - 7.45 (m, 3H); 7.53 (m,1H); 7.65 (m, 1H); 7.78 (m, 1H); 8.09 (d, 1H, J = 8.1 Hz); 8.18 (m, 2H); 8.24 (d, 1H, J = 8.1 Hz); 8.66 (dd, 1H, J = 7.4 Hz, J =1.5 Hz); 8.71 (dd, 1H , J = 5.1 Hz, J = 1.5 Hz), 9.13 (s, 1H); M.S. (C.I., NH_3): m/z 360 (M^++1).

11j: m.p. 257 - 259°C; I.R. (KBr) υ = 1190 cm^{-1} (SO_2); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm: 7.40 - 7.50 (m, 3H, $2H_{arom}$ + H_3); 7.57 (t, 1H, H_{arom}, J = 7.4 Hz); 7.62 (dd, 1H, H_8, J = 8.1 Hz, J = 4.4 Hz); 8.20 (d, 2H, H_{arom}, J = 7.4 Hz); 8.49 (dd, 1H, H_9, J = 8.1 Hz, J = 2.2 Hz); 8.75 (d, 1H, H_2, J = 4.4 Hz); 8.78 (d, 1H, H_4, J = 8.1 Hz); 9.19 (s, 1H, H_{10}); 9.21 (dd, 1H, H_7, J = 4.4 Hz, J = 2.2 Hz); M.S. (C.I., NH_3): m/z 361 (M^++1).



11j

(*Received in France* 14 *December* 1993; *accepted* 23 *January* 1994)