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$S_{RN}1$ REACTIONS IN IMIDAZO [1,2-*a*] PYRIDINE SERIES

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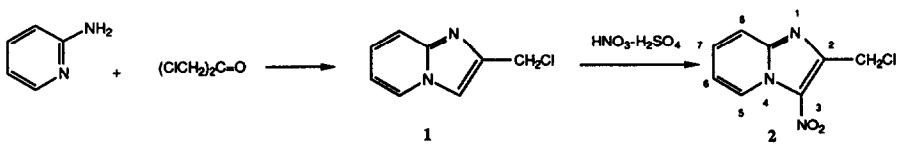
Summary : 2-Chloromethyl-3-nitroimidazo[1,2-*a*]pyridine is shown for the first time to react with 2-nitropropane salts by an $S_{RN}1$ mechanism to give excellent yield of isopropylidene derivative formed from the C-alkylation product by loss of nitrous acid.

The recent identification of benzodiazepine receptors[1] offers the possibility of correlating the pharmacological and clinical effects of existing hypnotics with the target sites of these molecules and thus with a putative mechanism of action. A new chemical series of compounds with the imidazopyridine structure has been recently synthetised[2] and shows a pharmacological and clinical profile with potential benefits over benzodiazepine. Indeed, these compounds may act preferentially at a subtype of the benzodiazepine receptor for which benzodiazepines have not a selectivity.[3]

In the course of extensive work in medicinal chemistry, our interest in the $S_{RN}1$ reactions for producing new pharmacological compounds[4] led us to study the reactivity of 2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine 2 which has new features with regard to previously studied nitroimidazoles: a fused pyridine ring, the nitro group in position 4 of the imidazole and the chloromethyl group in position 5 ortho to the nitro.

The substituted imidazo[1,2-*a*]pyridine **1** was obtained in 66% yield by reaction of 2-aminopyridine with dichloroacetone.[5] Nitration with HNO_3-H_2SO_4 led to the compound **2** (61% yield).[6]



1 2

The results of the reactions between 2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine **2** and the 2-nitropropane anion **3** in various experimental conditions are reported in the Table.

Table

Influence of experimental conditions on the reaction between **2** and **3**.

Assay[a]	Mol. equiv. of **3**	Solvent	Scavenger (mol. equiv.)	**5** % Yield[b]
1	2	CH_2Cl_2/H_2O	-	73
2	3	CH_2Cl_2/H_2O	-	95
3	3	CH_2Cl_2/H_2O	p-$NO_2C_6H_4NO_2$ (1)	73
4	3	CH_2Cl_2/H_2O	dark, O_2 (bubbling)	90
5	3	CH_2Cl_2/H_2O	(*tert*-Bu)$_2$NO$^{\cdot}$ (0.1)	15
6	2	DMF	-	94
7	2	DMF	$CuCl_2$ (6×10^{-4})	94
8	2	DMF	$CuCl_2$ (1.2×10^{-2})	88

[a]All reactions were performed during 24 h under argon and irradiation with two 60W fluorescent lamps using one equivalent of imidazopyridine **2**. [b]Product as per cent of theoritical yield relative to the electrophile as pure isolated product.

The above results show that the C-alkylation product **4** (Scheme) is not isolated under the reaction conditions and the formation of **5** can be rationalized in terms of an initial $S_{RN}1$ reaction to give **4** as highly reactive product which cleanly undergoes nitrous acid elimination leading to the ethylenic compound **5**.[7] Such behavior has already been observed in 5-nitroimidazole system, where elimination is more easy on position 2.[8]

The best yield is obtained under the usual conditions described by Kornblum[9] with DMF as solvent. The phase-transfer conditions (NBu_4OH 40% in water[10]) leading to **3** gave in CH_2Cl_2 if 3 equivalents of nitronate anion are used a similar yield.

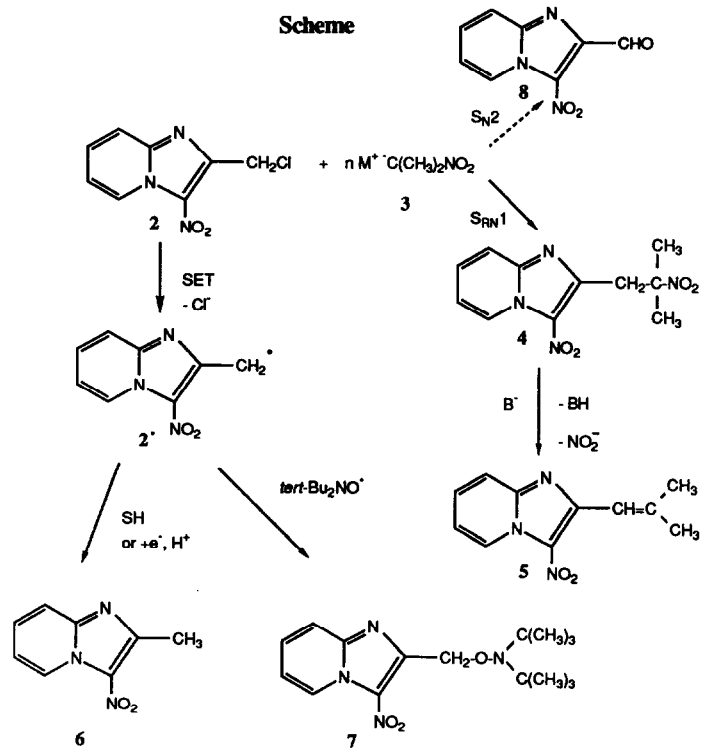
Although the $S_{RN}1$ mechanism seems most probable from structure of the product **5**, classical inhibition experiments[11] such as dark reaction, electron trapping, radical scavenging have been carried out.

The absence of light and dioxygen in excess have little if any effect on the yield of **5**. The small inhibition observed with p-dinitrobenzene may be due to strong electron affinity of **2** and of the intermediate dinitro radical-anion.The strong inhibition of the chain reaction by $CuCl_2$ described in the p-nitrobenzyl series[12] is not observed in the nitroimidazopyridine system but rings containing nitrogen are known to form complexes with cupric salts[13] which may change the concentration and the properties of the scavenger. Among the other criteria used for establishing the $S_{RN}1$ mechanism , the addition of 10 mole per cent of di-*tert*-butylnitroxide was shown to inhibit strongly the reaction by scavenging the free-radical intermediate **2**$^{\cdot}$ whose existence is also confirmed by the formation of the coupling product **7**[14] and the reduction product **6**.[15] In these reactions, it has not been possible to characterize the aldehyde **8** resulting from O-alkylation, since nitroimidazole aldehydes give untractable mixture[16] under these experimental conditions.

When the reaction was performed with the chloride **1** devoid of nitro group, neither C-alkylation nor O-alkylation derivatives are found in the reaction mixture, showing that the pyridine part of this substrate is not

enough electron-withdrawing for an $S_{RN}1$ reaction and that only an additional strong electron-acceptor group like the nitro group is able to promote this type of electron-transfer substitution reaction.

Scheme



In conclusion, all these results lead us to propose an $S_{RN}1$ mechanism for the reaction of 2-chloromethyl-3-nitroimidazo[1,2-*a*]pyridine **2** with 2-nitropropane anion **3** leading to excellent yield of isopropylidene derivative **5** by loss of nitrous acid from the C-alkylation product. The extension of this reaction to heterocyclic nitronate anions and the pharmacological studies of the resulting new nitroimidazo[1,2-*a*]pyridine compounds are in progress.

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REFERENCES AND NOTES

1 - (a) Moehler, H.; Okada, T. Life Sc. 1977, **20**, 2101-2110. (b) Squires, R. F.; Braestrup, C. Nature, 1977, **266**, 732-734.

2 - George, P.; Rossey, G.; Depoortere, H.; Monpon, B.; Allen, J.; Wick, A. in "Imidazopyridines in Sleep Disorders", Sauvanet, J. P.; Langer, S. Z. and Morselli, P. L.; Eds.; Raven Press, New York, 1988, pp. 11-23.

3 - Arbilla, S.; Depoortere, H.; George, P.; Langer, S. Z. Naunyn-Schmiedeberg's Arch. Pharmacol. 1986, **330**, 248-251.

4 - (a) Crozet, M. P.; Surzur, J.-M.; Vanelle, P.; Ghiglione, C.; Maldonado, J. Tetrahedron Lett. 1985, **26**, 1023-1026. (b) Crozet, M. P.; Jentzer, O.; Vanelle, P. Tetrahedron Lett. 1987, **28**, 5531-5534. (c) Crozet, M. P.; Vanelle, P.; Jentzer, O.; Bertrand, M. P. Heterocycles, 1989, **28**, 849-855.

5 - Rival, Y. Thesis of Doctorat ès-Sciences Pharmaceutiques, Toulouse, 1987.

6 - Gueiffier, A. Thesis of Doctorat en Pharmacie, Montpellier, 1969.

7 - **5**, Orange solid, F = 167°C (ethanol), ^{1}H NMR ($CDCl_3$) δ 2.09 (d, J = 1 Hz, CH_3); 2.34 (d, J = 0.8 Hz, CH_3); 7.08 (m, CH); 7.19 (td, J = 7.0 Hz and J = 1.1 Hz, H_7); 7.61 (ddd, J = 9.0 Hz, J = 7.0 Hz and J = 1.1 Hz, H_6); 7.73 (dt, J = 9.0 Hz and J = 1.1 Hz, H_8); 9.47 (dt, J = 7.0 Hz and J = 1.1 Hz, H_5).

8 - (a) Crozet, M. P. ; Vanelle, P. in "Substituent Effects in Radical Chemistry", Viehe, H. G.; Janousek, Z.; Merenyi, R.; Eds; Nato Asi Series, D. Reidel Publishing Company, Dordrecht, 1986, Vol. 189, pp. 335-338. (b) Crozet, M. P. ; Vanelle, P. Tetrahedron, 1989, **45**, 5477-5484. (c) Crozet, M. P.; Vanelle, P.; Jentzer, O.; Maldonado, J. Tetrahedron Lett. 1990, in press.

9 - Kornblum, N.; Carlson, S. C.; Widmer, J.; Fifolt, M. J.; Newton, B. N.; Smith, R. G. J. Org. Chem. 1978, **43**, 1394-1399.

10 -Burt, B. L.; Freeman, D. J.; Gray, P. G.; Norris, R. K.; Randles, D. Tetrahedron Lett. 1977, 3063-3066.

11 -Chanon, M.; Tobe, M. L. Angew. Chem. Int. Ed. Engl. 1982, **21**, 1- 23.

12 -Kornblum, N.; Michel, R. E.; Kerber, R. C. J. Am. Chem. Soc.1966, **88**, 5662-5663.

13 -(a) Grimmett, M. R. Adv. Heterocycl. Chem. 1970, **12**, 103-183. (b) Massey, A. G. in "The Chemistry of Copper, Silver and Gold", Trotman-Dickenson, A. F.; Ed.; Pergamon Press, Oxford, 1973, Ch. 27, pp.1-78.

14 -**7**, Orange solid, F = 112 °C, ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 18H, $[(CH_3)_3C)_2]$; 5.42 (s,CH_2); 7.34 (td, J = 7.0 Hz and J = 1.1 Hz, H_7); 7.70 (ddd, J = 9.0 Hz, J = 7.0 Hz and J = 1.1 Hz, H_6); 7.88 (dt, J =9.0 Hz and J = 1.1 Hz, H_8); 9.46 (dt, J = 7.0 Hz and J = 1.1 Hz, H_5). MS: M^+= 321, m/e (%): 320 (4); 249 (6); 177 (39); 160 (20); 144 (35); 118 (8); 88 (45); 79 (10); 78 (46); 57 (100).

15 -**6**, Orange solid, F = 121 °C, ^{1}H NMR ($CDCl_3$) δ 2.88 (s, 3H); 7.34 (td, J = 7.0 Hz and J = 1.1 Hz, H_7); 7.70 (ddd, J = 9.0 Hz, J = 7.0 Hz and J = 1.1 Hz, H_6); 7.88 (dt, J = 9.0 Hz and J = 1.1 Hz, H_8); 9.46 (dt, J = 7.0 Hz and J = 1.1 Hz, H_5). MS: M^+ = 177; m/e (%): 178 (6); 177 (47); 119 (23); 90 (19); 79 (16); 78 (100); 57 (17); 50 (28).

16 - Vanelle, P. Thesis of Doctorat ès-Sciences Physiques, Marseille, 1987.

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