Tetrahedron Letters,Vol.30,No.45,pp 6169-6172,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF POLYIMIDAZOLES AS BIOMIMETIC LIGANDS FOR METALLOPROTEIN ACTIVE SITE MODELING.

E. MULLIEZ

Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques,
Université René Descartes, URA 400 CNRS,
45 rue des Saints-Pères 75270 Paris Cedex 06, France.

Abstract : The synthesis of potentially biomimetic tri and tetradentate molecules containing two to four imidazoles rings is described.

In recent years, several organometallic complexes carrying imidazole-containing ligands have been described as models for the active site of metalloproteins such as carbonic anhydrase [1], hemerythrin [2], hemocyanin[3], urease[4], and others(5).

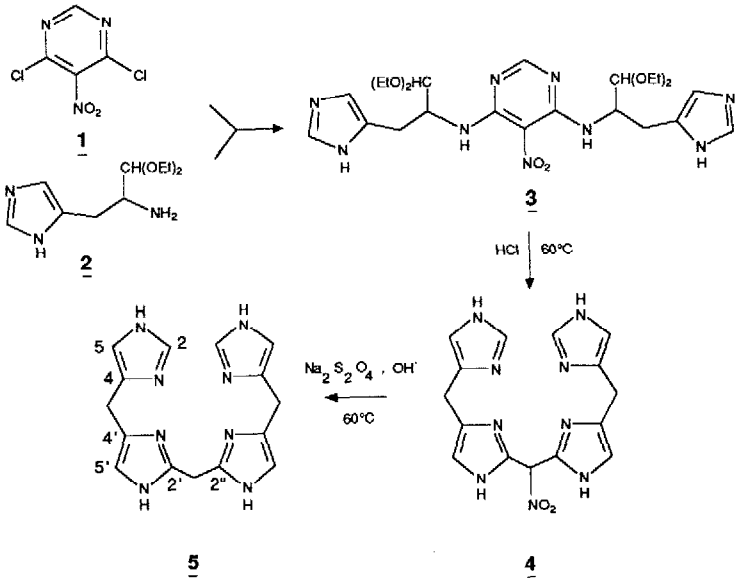
In the case of lipoxygenase, a non heme iron dioxygenase, EPR[6] and recent EXAFS data[7] suggest that the iron is in an axial environment involving four imidazole nitrogens in a plane and two/one carboxylato ligand(s) in apical position(s).

In the search for a tetraimidazole ligand which could mimic in part the active site of lipoxygenase we have found an easy and versatile approach to polydentate ligands containing two to four imidazoles.

Several years ago, an efficient synthesis of the bidentate ligand bis [imidazol-2 yl]methane, 2-BIM, was reported[8]. Starting from commercially available 4,6-dichloro-5-nitropyrimidine (**1**) and amino acetaldehyde dimethylacetal, 2-BIM was synthesized in three steps with an overall yield of 46%. We reasoned that this synthesis should not be restricted to the use of aminoacetaldehyde acetal (i.e. glycinal acetal) and could be extended to virtually any α-amino aldehyde acetal and particularly to the acetal of histidinal (**2**) as shown in Scheme 1.

Accordingly, histidinal diethylacetal[9], **2**, (8,5 g, 40 mmoles) and triethylamine (8,5 ml) in EtOH at 5°C react with **1** (3,9 g, 20 mmoles) to afford the pale yellow nitro pyrimidine **3**, mp : 220-221°C (7,7g, 70% yield after recrystallization in CH_2Cl_2, not optimized). Recrystallized **3** undergoes cyclization in concentrated HCl (1 hour at 60°C) to give a quantitative yield of golden yellow **4**. The latter was not purified and was smoothly reduced by a 3-fold excess of sodium

SCHEME 1



SCHEME 2

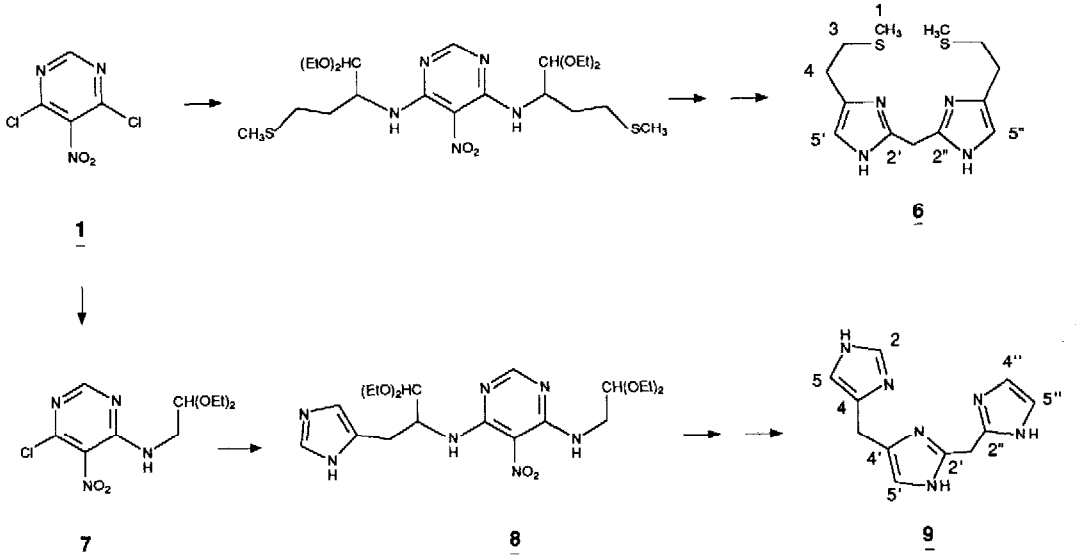


Table 1 : Analytical and spectroscopic properties of polyimidazoles ligands.

Polyimidazole	mp(C°) (a)	elemental analysis	mass spectrometry m/z (b)	^{1}H NMR 90 MHz δ (ppm) (c)	^{13}C NMR 62.5 MHz δ (ppm) (d)
		5 , 4 H_2O	309 (100)	***CD_3OD***	***DMSO*** (d_6)
		calc. *found*	229 (5)	7.50 (d,(1.2)2H) H_2	143.45 $C_{2'}$
		C 47.36 47.69	163 (32)	6.73 (m,2H) H_5 ($H_{5'}$)	135.19 C_4($C_{4'}$)
5	170[a]	H 6.31 6.34	149 (5)	6.61 (m,2H) $H_{5'}$ (H_5)	134.95 $C_{4'}$(C_4)
	recryst. H_2O	N 29.47 29.14		4.06 (s,2H) $CH_{2\ 2'2''}$	134.82 C_2
				3.81 (s, 4H) $CH_{2\ 44'}$	117.76 C_5($C_{5'}$)
					117.19 $C_{5'}$(C_5)
					28.08 $C_{2'2''}$
					25.02 $C_{44'}$
		6, H_2O	227 (100)	***$CDCl_3$***	***CD_3OD***
	115-116	*calc.* *found*	251 (16)	10.23 (s, 2H) NH	144.51 $C_{2'}$
	recryst.	C 49.68 49.82	157 (28)	6.73 (s, 2H) $H_{5'}$	137.36 $C_{4'}$
6	H_2O/CH_3COCH_3	H 7.00 6.97	143 (45)	4.25 (s, 2H) $CH_{2\ 2'2''}$	118.14 $C_{5'}$
	1/2	N 17.83 17.81		2.76 (m, 8H) H_3, H_4	34.82 C_3
		S 20.38 19.79		2.06 (s, 6H) H_1	28.55 $C_{2'2''}$
					28.11 C_4
					15.41 C_1
		9	229 (100)	***CD_3OD***	***CD_3OD***
		calc. *found*	160 (9)	7.56 (d,(1.2) 1H) H_2	145.13 $C_{2'}$($C_{2''}$)
		C 57.89 57.63	148 (24)	6.95 (s 2H) $H_{4''}$,$H_{5''}$	144.62 $C_{2''}$($C_{2'}$)
9	238-240	H 5.26 5.46		6.80 (m, 1H) H_5($H_{5'}$)	136.78 C_4 ($C_{4'}$)
	recryst. H_2O	N 36.84 36.61		6.70 (m, 1H) $H_{5'}$(H_5)	136.51 $C_{4'}$(C_4)
				4.11 (s, 2H) $CH_{2\ 2'2''}$	135.95 C_2
				3.85 (s, 2H) $CH_{2\ 44'}$	122.86 $C_{4''}$,$C_{5''}$
					118.43 C_5 ($C_{5'}$)
					118.25 $C_{5'}$ (C_5)
					28.47 $C_{2'2''}$
					25.63 $C_{44'}$

(a) melting points not corrected. **5** melts at 170°C giving a solid mp > 260°C.
(b) m/z, relative intensity in parentheses. **5** exact mass : 309. 15761 (calc.), 309. 15167 (found)
(c)δ in ppm relative to TMS as internal standard. Atom numbering as in Scheme 1 and 2.. s : singlet, d : doublet, m : multiplet , J,Hz in parentheses
(d)δ in ppm relative to CD_3OD or DMSO (d_6) Tentative assigment. Atom numbering as in Scheme 1 and 2.

dithionite in 3M NaOH solution (1 hour at 60°C) to give 4.2 g of off-white crystalline bis [(imidazol-4 methyl)-4' imidazol-2'-yl] methane, **5** (Table 1) in an overall yield of 68% starting from **1**.

As anticipated, this straightforward synthesis could be used to prepare other polydentate ligands as shown in Scheme 2.

Starting from methioninal diethylacetal[10], the mixed imidazole-thioether tetradentate, bis [(methylthio- ethyl)-4 imidazol-2 yl] methane, **6**, Table 1, was synthesized in a 77% yield.

Addition of an ethanolic solution of one equivalent of α-amino acetaldehyde dimethylacetal and triethylamine (1:1.5) to **1**, affords the mono-substituted nitropyrimidine **7**, as yellow needles, mp = 62-63°C (60% yield after silica-gel flash column chromatography). **7** can undergo a second substitution with **2**, giving the mixed nitro pyrimidine **8**, which, likewise, produced the tris imidazole, [(imidazol-2 methyl)-2' (imidazol-4" methyl)-4'] imidazole, **9**, Table 1, in a 55% overall yield from **1**.

Spectroscopic and analytical data of the polyimidazoles are gathered in Table 1.

We are currently using iron complexes of the tetraimidazole **5** for lipoxygenase active site modeling.

Acknowlegments : I thank Professor J.C. Chottard and Dr. G. Guillot-Edelheit for fruitful discussions.

References and notes

(1) R. BRESLOW, J.T. HUNT, R. SMILEY and T. TARNOWSKI, *J.Am.Chem.Soc.* **105**, 5337-5342 (1983).
(2) S.M. GORUN and S.J. LIPPARD, *Inorg.Chem.* **27**, 149-156 (1988).
(3) W.B. TOLMAN, R.L. RARDIN and S. J. LIPPARD, *J.Am.Chem.Soc.* **111**, 4532-4533 (1989)
(4) R.M. BUCHANAN, M.S. MASHUTTA, K.J. OBERHAUSEN, J.F. RICHARDSON, D. LI AND D.N. HENDRICKSON, *J.Am.Chem.Soc.* **111**, 4498-4500 (1989)
(5) T.G. TRAYLOR, K.W. HILL, Z.Q. TIAN, A.L.RHEINGOLD, J. PEISACH and J. Mc CRACKEN, *J.Am.Chem.Soc.* **110**, 5571-5573 (1988)
(6) J.J.M.C. de GROOT, G.A. VELDINK, J.F.G. VLIEGENTHART, J. BOLDINGH, R. WEVER AND B.F. VAN GELDER, *Biochim.Biophys.Acta*, **377**, 71-79 (1975)
(7) S. NAVARATNAM, M.C. FEITERS, M. AL-HAKIM, J.C. ALLEN, G.A. VELDINK and J.F.G. VLIEGENTHART, *Biochim..Biophys.. Acta*, **956**, 70-76 (1988)
(8) M. JOSEPH, T. LEIGH AND M.L. SWAIN, *Synthesis*, 459-460 (1977)I
(9) E.J. ADAMS, *J. Biol.Chem.* **217**, 325-331 (1955)
(10) Methioninal diethyl acetal was prepared from the aldehyde hydrate [9] by ethyl orthoformiate, ammonium chloride acetalization $Eb_{0.5}$= 72-74°C Yield: 35%.

(Received in France 1 August 1989)