REACTIVITY OF IMIDAZO[1,2-b]PYRIDAZINE 1-OXIDES

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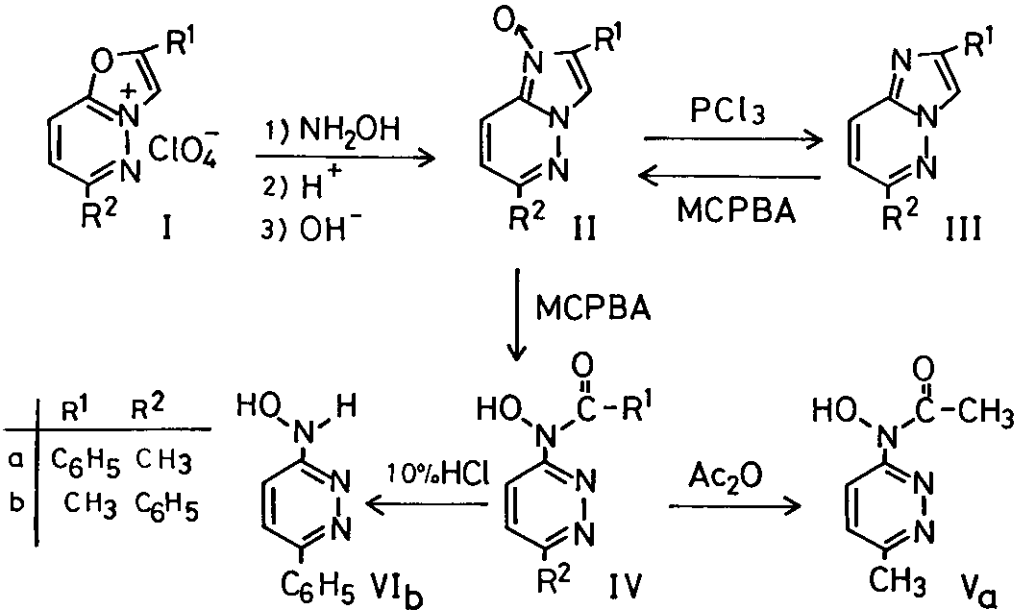
The treatment of either imidazo[1,2-b]pyridazines(III) or their 1-oxides(II) with excess organic peracid resulted in the oxidative cleavage of imidazole moiety to give 3-(N-acylhydroxylamino)pyridazines(IV). The bromination and nitration of II gave the corresponding 3-substituted N-oxides(VII,IX,X, and XI). Rearrangement reaction of II with phosphoryl chloride or acetic anhydride afforded the deoxygenated 7-substituted imidazopyridazines, XII and XIII, respectively.

In the course of our studies on the synthesis and reaction of pi-deficient heteroaromatics, it was found that oxazolo[3,2-b]-pyridazinium perchlorates (I)[1] reacted with hydroxylamine to furnish imidazo[1,2-b]pyridazine 1-oxides (II),[2] which could be potential precursors for physiologically active imidazo[1,2-b]-pyridazines with additional functional groups on the ring.[3] As very few reports have been published on the reactivity of this

pi-excessive azole N-oxides,[4] we have now examined the reactivity of this system toward a couple of reagents.

Further oxidation of the N-oxide (IIb) with m-chloroperbenzoic acid (MCPBA) afforded 3-(N-acetylhydroxylamino)-6-phenylpyridazine (IVb)[38% ; mp 215-216°; IR ν_{max}^{KBr} (cm^{-1}) : 3250, 1695; NMR δ (ppm in $CDCl_3$) : 7.56 (1H, d, J=9Hz), 8.80 (1H, d, J=9Hz), 9.62 (1H, s,OH)] conceivably by oxidation at the 3-position and ring-opening with subsequent decarboxylation. The same compound (IVb) was also formed as the major product by the direct oxidation of the azole (IIIb), the deoxygenated product of IIb with phosphorous trichloride, in the same manner with excess MCPBA. This fact indicates that electrophilic reagents attack at the 3-position of imidazo[1,2-b]pyridazine 1-oxide system. Hydrolysis of IVb with



Scheme 1

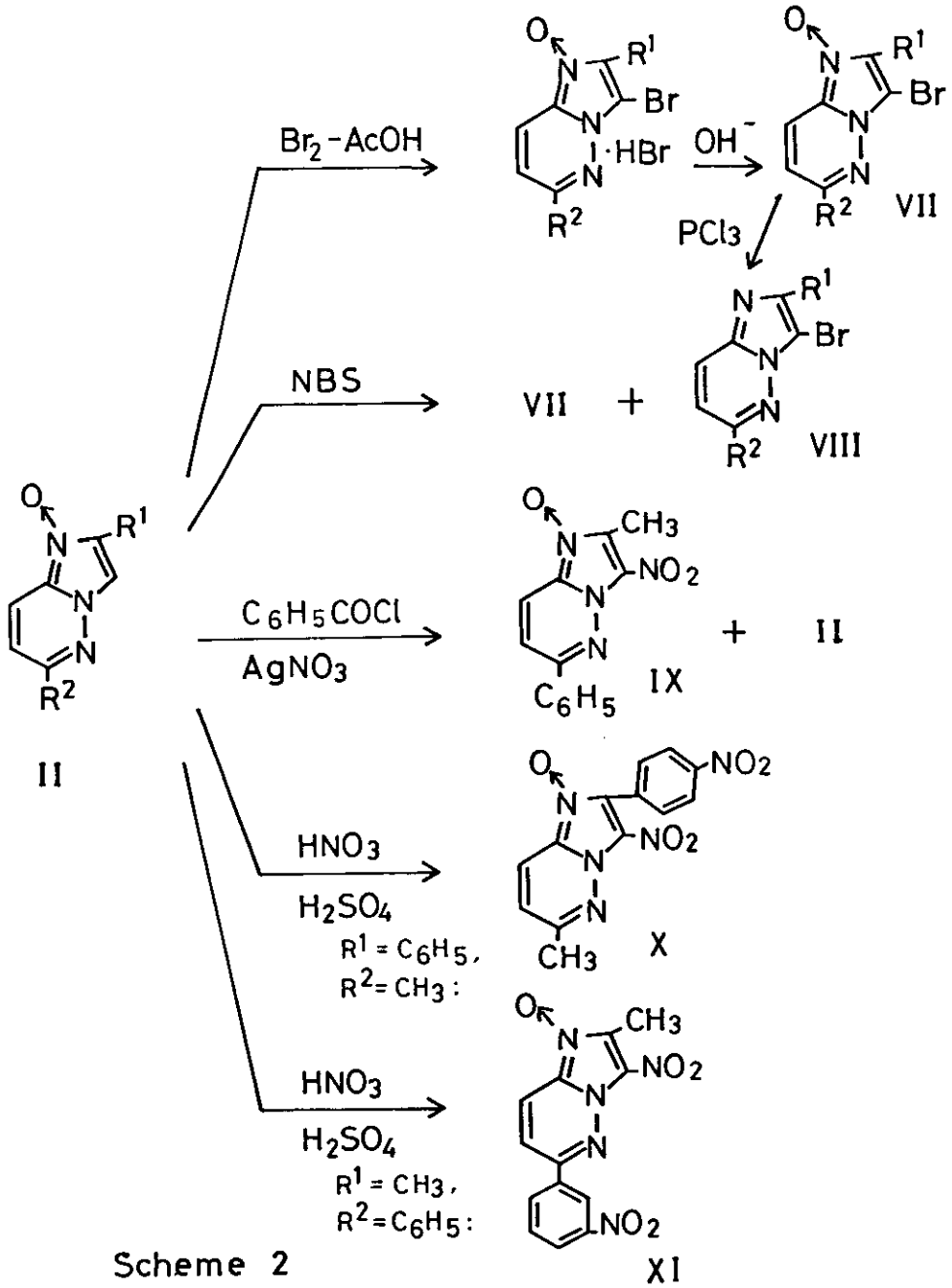
10% HCl gave 3-hydroxylaminopyridazine (VIb) [80% ; mp 185-186°; IR ν_{max}^{KBr} (cm^{-1}) : 3310, 3080 ; NMR δ (ppm in CD_3OD) : 7.40 (1H, d, J=9HZ), 7.75 (1H, d, J=9Hz)]. Heating of the benzamide (IVa) in acetic anhydride gave the corresponding acetamide (V).

Bromination of the N-oxide (IIa) with bromine in acetic acid at room temperature gave the hydrobromide of 3-bromo-N-oxide (VIIa·HBr) [57% ; mp 147-148° ; NMR δ (ppm in CF_3COOH) : 2.90 (3H, s), 7.73 (1H, d, J=10Hz), 8.34 (1H, d, J=10Hz)], which was converted with 5% NaOH into the free base (VIIa) [mp 190-191° ; NMR δ (ppm in $CDCl_3$) : 2.68 (3H, s), 6.97 (1H, d, J=10Hz), 8.21 (1H, d, J=10Hz)]. The 3-bromo-N-oxide (VIIa) was also obtained by heating of a solution of IIa and N-bromosuccinimide (NBS) in chloroform in 42% yield together with the deoxygenated 3-bromo-compound (VIIIa) [21% ; mp 180-180.5° ; NMR δ (ppm in $CDCl_3$) : 2.64 (3H, s), 6.94 (1H, d, J=10Hz), 7.80 (1H, d, J=10Hz)]. The similar reaction of IIb with NBS afforded VIIb [79% ; mp 207-208°; NMR δ (ppm in $CDCl_3$) : 2.58 (3H, s), 7.42 (1H, d, J=10Hz), 8.22 (1H, d, J=10Hz)] together with a trace amount of VIIIb [mp 120-120.5° ; NMR δ (ppm in $CDCl_3$) : 2.50 (3H, s), 7.48 (1H, d, J=10Hz), 7.86 (1H, d, J=10Hz)]. 3-Bromoimidazopyridazine 1-oxides (VII) were smoothly deoxygenated by heating with phosphorous trichloride in chloroform to give VIII.

Nitration of the N-oxide (IIb) with benzoyl chloride-silver nitrate in chloroform at room temperature gave after 40 days 3-nitro compound (IX) [11% ; mp 221-222°(dec.) ; NMR δ (ppm in DMSO-d_6) : 2.70 (3H, s), 8.23 (1H, d J=10Hz), 8.60 (1H, d, J=10Hz), 7.53-7.70 (3H, arom.), 8.10-8.30 (2H, arom.)] and the starting material was recoverd in 70% yield. Nitration of IIa and IIb with HNO_3-H_2SO_4 at room temperature gave after 2 days dinitro compound, X [20% ; mp 239-249°(dec.) ; NMR δ (ppm in DMSO-d_6) : 2.71 (3H, s), 7.61 (1H, d, J=10Hz), 8.11 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz), 8.51 (1H, d, J=10Hz)] and XI [13% ; mp 237-238°(dec.) ; NMR δ (ppm in CF_3COOH) ; 3.13 (3H, s), 7.75-8.05 (3H, arom.), 8.17 (1H, d, J=10Hz), 8.33-8.46 (1H, arom.) 8.74 (1H, d, J=10Hz)], respectively.

Heating of the N-oxides, IIa and IIb, in refluxing phosphoryl chloride for 1 hour afforded the deoxygenated 7-chloro compounds, XIIa [46% ; mp 171-173° ; NMR δ (ppm in $CDCl_3$) : 7.90 (1H, s, C_8-H), 8.15 (1H, s, C_3-H)] and XIIb [41% ; mp 134-135° ; NMR δ (ppm in $CDCl_3$) :7.75 (1H, s, C_3-H), 7.96 (1H, s, C_8-H)] together with the deoxygenated IIIa (16% yield) and IIIb (14% yield), respectively. The NMR spectra of 7-chloroimidazopyridazines (XII) showed two singlet peaks at around 8 ppm, indicating that substitution reaction occurred at the 7-position.[5)]

Heating of the N-oxide (IIa) in refluxing acetic anhydride gave 7-acetoxyimidazo[1,2-b]pyridazine, XIII [63% ; mp 136-137° ; IR ν_{max}^{KBr} (cm^{-1}) : 1780 ; NMR δ (ppm in $CDCl_3$) : 2.35 (3H, s), 2.42 (3H, s), 7.65 (1H, s, C_8-H), 8.14 (1H, s, C_3-H)] in good yield. The same reaction of IIb gave 2-acetoxymethyl derivative, XIV


Br2-AcOH
HBr
OH⁻
PCl3
NBS
VII
+
VIII
C6H5COCl
AgNO3
IX
+
II
II
HNO3
H2SO4
R1 = C6H5,
R2 = CH3 :
X
HNO3
H2SO4
R1 = CH3,
R2 = C6H5 :
XI

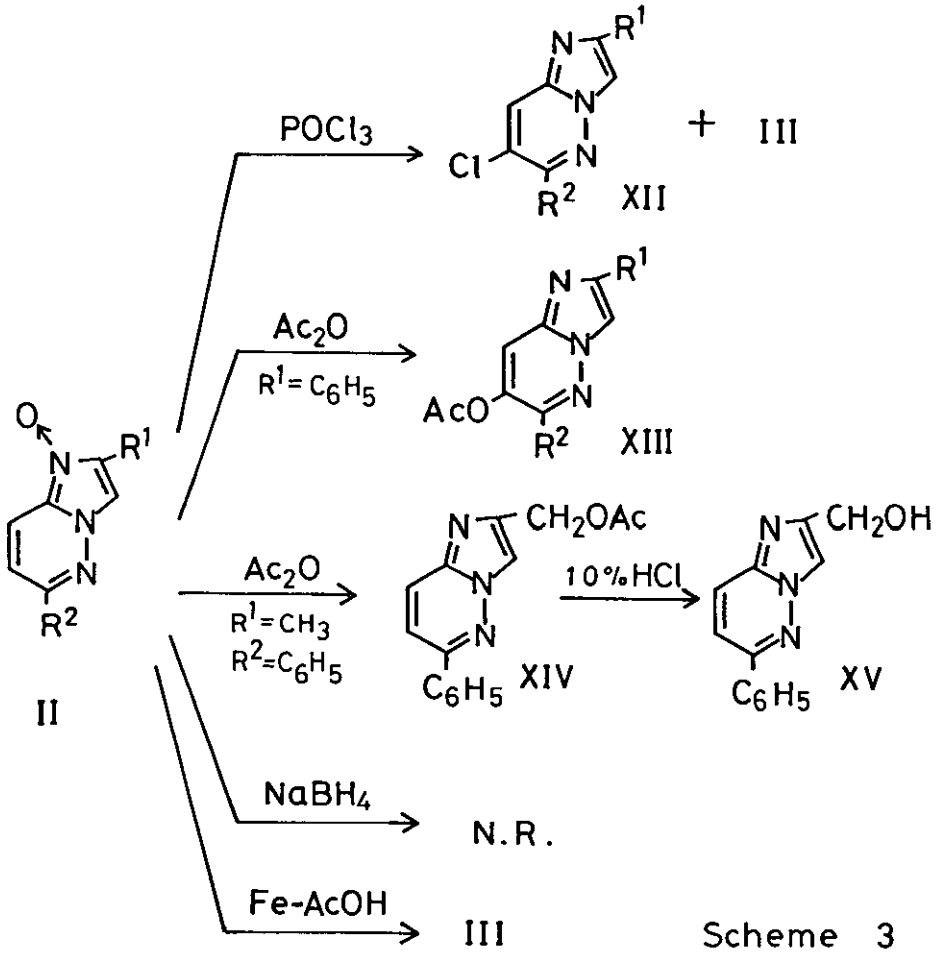
Scheme 2

[70% ; mp 81.5-82° ; IR ν_{max}^{KBr} (cm^{-1}) : 1750, 1740 ; NMR δ (ppm in $CDCl_3$) : 2.13 (3H, s), 5.31 (2H, s), 7.47 (1H, d, J=10Hz), 7.94 (1H, D, J=10Hz), 8.02 (1H, s)], which was hydrolysed into hydroxymethyl derivative, XV [65% (from IIb); mp 147-147.5° ; IR ν_{max}^{KBr} (cm^{-1}) : 3180 ; NMR δ (ppm in $CDCl_3$) : 3.94 (1H, s, OH), 4.90 (2H, s), 7.42 (1H, d, J=10Hz), 7.92 (1H, d, J=10Hz)] by heating with 10% HCl for 4 hours.

Attempted reduction of the N-oxide (IIa) with $NaBH_4$ in ethanol failed, however, Fe dust in the presence of acetic acid was effective at room temperature to deoxygenate IIa into IIIa in 83% yield.

Other imidazopyridazine 1-oxides (II, $R^1=C_6H_5$, $R^2=Cl$; $R^1=R^2=C_6H_5$) reacted in the similar manner with such reagents as bromine, NBS, phosphoryl chloride, and acetic anhydride.

It is well known in the literature[7] that azine N-oxides react with electrophilic reagents readily in contrast to the case of the corresponding azines. Tišler and coworkers examined some electrophilic substitution reaction on imidazo[1,2-b]pyridazine itself and observed formation of the 3-bromo- and 3-nitro-substituted products under very mild conditions.[6a] The authors also recognized that bromination of the azoles (III) with NBS more smoothly proceeded than that of the azole N-oxides (II). It is noteworthly that electrophilic substitution reaction of imidazo-[1,2-b]pyridazine 1-oxides (II) require much severer conditions than those of the corresponding azoles (III).


POCl3
Cl
R2
XII
+ III
Ac2O
R1= C6H5
AcO
XIII
Ac2O
R1=CH3
R2=C6H5
CH2OAc
C6H5
XIV
10%HCl
CH2OH
XV
II
NaBH4
N.R.
Fe-AcOH
III

Scheme 3

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5. The C_7-H and C_8-H proton signals of imidazo[1,2-b]pyridazines were observed at around 6.83-6.92 and 7.74-7.97 ppm, respectively, by Tišler and coworkers.[6)]
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