SYNTHESIS OF s-TRIAZOLO[1,5-a]PYRIDINE 1-OXIDES

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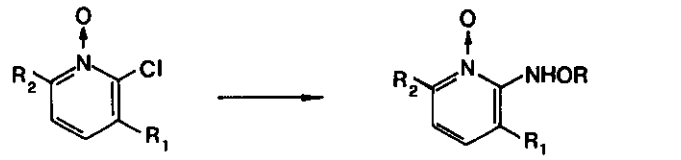
Abstract - The preparation of several hydroxylaminopyridines is described. From 1-amino-2-hydroxyimino-1,2-dihydropyridine (8) s-triazolo[1,5-a]pyridine 1-oxides (9) were synthesized and from 3-hydroxylamino-6-chloropyridazine (11) an imidazo-[1,2-b]pyridazine 1-oxide derivative (12) was prepared.

Until recently, N-oxides of azoloazines with bridgehead nitrogen were not known. Among the first, compounds with the N-oxide function in the six-membered ring of these bicycles were synthesized.[1-4] Later, 3-oxides of azoloazines were prepared [5] and we have developed a useful new method for the synthesis of 2-unsubstituted azoloazines by oxidative cyclization of hydroxyiminomethyleneaminoazines.[6,7] Quite recently, the first representatives of 1-oxides were obtained. Imidazo[1,2-b]pyridazine 1-oxides were synthesized from oxazolo[3,2-b]pyridazinium perchlorates and hydroxylamine,[8,9] whereas 2-phenylimidazo[1,2-a]pyridine 1-oxide, a rather sensitive compound, was obtained in admixture with other products from 2-halo-1-phenacylpyridinium salt and hydroxylamine.[10]

In view of these results we like to report on a new synthetic approach for the preparation of s-triazolo[1,5-a]pyridine 1-oxides (9). For the devised strategy azinyl hydroxylamines are the most appropriate as starting material. Few compounds of this class are known and most of them were prepared by partial reduction of the corresponding nitro compounds. In view of the formation of by-products in these reductions we preferred the introduction of a hydroxylamino group by displacement reactions. Preliminary results have shown that in the azine series one must have a good leaving group (like halogen or alkylthio group), preferentially activated by other substituents, in order that the reaction proceeds smoothly. The reactivity of the group to be displaced by hydroxylamine or O-ben-

zylhydroxylamine can be also enhanced either by N-oxydation, quaternization or N-amination of the ring nitrogen. For example, 2,6-dichloropyridine 1-oxide (1, R_1 = H, R_2 = Cl) reacted with free hydroxylamine at room temperature to give after 6 days the corresponding 2-hydroxylamino derivative (2, R = R_1 = H, R_2= Cl) in 24 % yield, mp 130-132° (from ethanol and n-hexane, 3 : 1); m/e 160 (M^+). In a similar manner reacted 2-chloro-3-nitropyridine 1-oxide (1, R_1 = NO_2, R_2 = H) with O-benzylhydroxylamine to give after 14 h at room temperature compound 2 (R = CH_2Ph, R_1 = NO_2, R_2 = H), mp 120-123° (from carbon tetrachloride). On the other hand, the reaction between 3 and O-benzylhydroxylamine afforded compound 4 in 25 % yield, mp 144-145° (from 1,2-dimethoxyethane and diethyl ether). The preferential displacement of the fluorine atom at position 3 rather than of the nitro group at position 4 is rather surprising. Normally a greater reactivity towards nucleophiles of a para standing leaving group of pyridine N-oxides is observed and, in addition to this, the observed order of reactivity is NO_2>halogen>alkoxy group> amino group.[11] For the described reaction, we ascribe the diminished reactivity of the nitro group as a result of additional stabilization of the molecule through the canonical form 3b.



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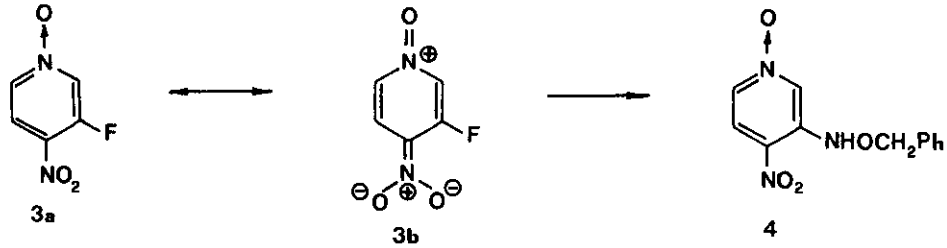

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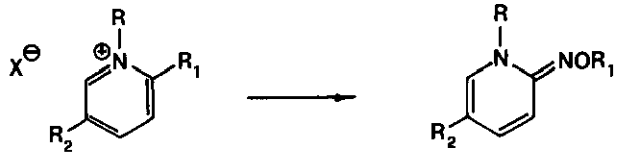

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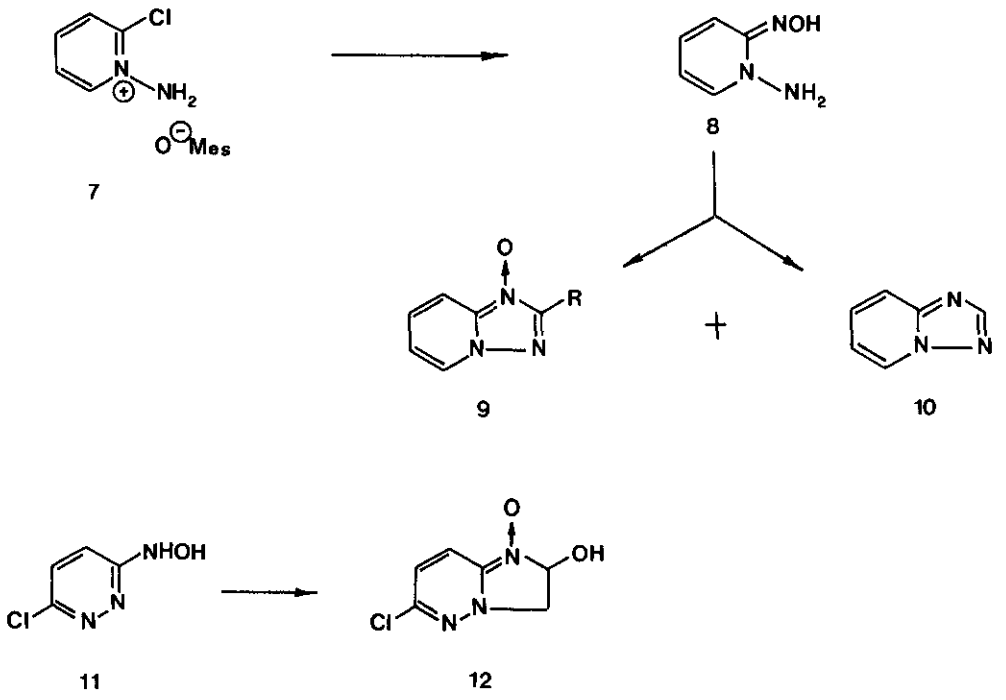
Quaternized halopyridines reacted with hydroxylamine or O-benzylhydroxylamine to give the corresponding oxyimino derivatives in moderate to good yields. For example, 1-benzyl-2-bromopyridinium bromide (5, R = CH_2Ph, R_1 = X = Br, R_2 = H) was transformed with hydroxylamine after 20 min at room temperature into the hydroxyimino compound 6 (R = CH_2Ph, R_1 = R_2 = H) in 62 % yield, mp 148-150° (from ethanol and n-hexane, 6 : 1); m/e 200 (M^+) and nmr δ ($CDCl_3$) 6.9 (m, Ph), 6.45 (deg. dd, H_6), 6.30 (m, H_3 and H_4), 5.20 (ddd, H_5), 4.48 (s, CH_2), $J_{5,6}$ = 5.5, $J_{4,5}$ = $J_{3,4}$ = 8.0, $J_{4,6}$ = 3 Hz. The above mentioned bromo compound, when treated with O-benzylhydroxylamine at room temperature for 80 min, afforded after extraction of the reaction mixture with chloroform, saturation of the extracts with hydrogen chloride and washing with water and evaporation of the solvent an oily residue which was sublimed first at 110°/4 mm and thereafter at 180°/4 mm to give the benzyloxyimino derivative 6 (R = R_1 = CH_2Ph, R_2 = H) in 42 % yield; m/e 290 (M^+). In a similar manner, from 1-ethyl-2-chloro-5-nitropyridinium tetrafluoroborate (5, R = Et, R_1 = Cl, R_2 = NO_2, X = BF_4) the corresponding oxyimino derivatives 6 (R = Et, R_1 = H, R_2 = NO_2), mp 171 - 175° (purified by TLC on Kieselgel 60 F254 and eluted with 1,2-dimethoxyethane); m/e 183 (M^+); and 6 (R = Et, R_1 = CH_2Ph, R_2 = NO_2), bp 190°/4 mm; m/e 273 (M^+), were obtained in 47 % and 90 % yield, respectively.

1-Amino-2-chloropyridinium mesylate (7) [12] was treated with hydroxylamine for 71 hours at room temperature. Upon extraction of the alkaline solution with chloroform 1-amino-2-hydroxyimino-1,2-dihydropyridine (8) was obtained in 61 % yield, mp 118-121° (from chloroform and carbon tetrachloride, 1 : 4); m/e 125 (M^+), and nmr δ ($CDCl_3$) 6.75 (dd, H_6), 6.35 (ddd, H_4), 6.28 (dd, H_3), 5.10 (ddd, H_5), $J_{5,6}$ = 6.0, $J_{4,5}$ = $J_{3,4}$ = 9.0, $J_{3,6}$ = 1.0, $J_{3,5}$ = 2.0 and $J_{4,6}$ = 1.5 Hz. This compound, when treated with boiling formic acid for 3 hr, afforded after evaporation of the reaction mixture to dryness and extraction of the residue with diethyl ether s-triazolo|1,5-a|pyridine (10) [13] in 4 % yield. From the aqueous phase its 1-oxide (9, R = H) was obtained in 29 % yield, mp 104° (loss of water from the monohydrate) and 165-168° (from benzene and chloroform, 5 : 1); m/e 135 (M^+) and nmr δ ($CDCl_3$) 8.2 (s, H_2), 8.05 (ddd, H_5), 7.63 (dd, H_8), 7.25 (ddd, H_7), 6.8 (ddd, H_6), $J_{5,6}$ = 7.0, $J_{6,7}$ = $J_{7,8}$ = 8.0, $J_{6,8}$ = $J_{5,7}$ = 2.0 Hz. At 196° (in autoclave) only 10 was formed in 48 % yield, whereas from 8 and N,N-dimethylformamide dimethylacetal after 13 hr under reflux only the 1-oxide 9 (R = H) was obtained in 54 % yield. In a simi-



lar manner, compound 8 reacted with trifluoroacetic anhydride to give 9 (R = CF_3) in 17 % yield, mp 189-191° (from chloroform and diethyl ether, 1 : 1; m/e 203 (M^+).

N-(6-Chloro-3-pyridazinyl)hydroxylamine (11), mp 142-143°, prepared from 3,6-dichloropyridazine and ethanolic hydroxylamine after 6 hr under reflux, was treated with bromoacetaldehyde at room temperature for 14 hr. The reaction mixture was extracted with chloroform to give 2-hydroxy-6-chloro-2,3-dihydroimidazo-[1,2-b]pyridazine 1-oxide (12) in 20 % yield, mp 165-166° (from ethanol); m/e 187 (M^+) and nmr δ (CD_3OD) 6.75 (s, H_7 and H_8), 5.50 (m, H_2), 3.93 (m, 3-CH_2), J_{gem} = = 2.0 Hz.

All above mentioned 1-oxides gave a positive test for the presence of a N-oxide group [14] and satisfactory analytical data have been obtained for all compounds described in this communication.

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