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BH_3: THF REDUCTION OF 3-METHYLISOXAZOLO[4,5-c] PYRIDINES

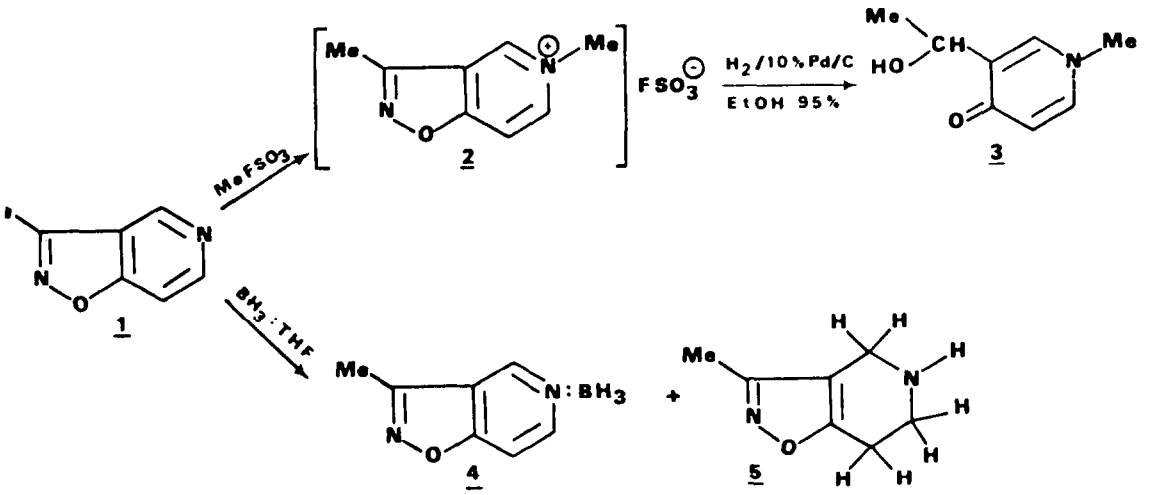
G.Adembri, A.Camparini, F.Ponticelli
Istituto di Chimica Organica dell'Università, Siena, Italy
P.Tedeschi *
Centro di studio del C.N.R. sulla chimica e la struttura dei composti eterociclici e loro applicazioni, c/o Istituto di Chimica Organica dell'Università, Firenze, Italy

Summary: 3-Methylisoxazolo[4,5-c]pyridine 1 on reduction with BH_3:THF gave, via the isolable complex 4, the tetrahydroisoxazolopyridine 5. The presence of two chlorine atoms at the 4 and 6 positions directed borane attack to the isoxazole ring, yielding the aminoethylpyridine 8. Both types of reduction were obtained with 6-chloroisoxazolo[4,5-c]pyridine 7.

Strong synthetic and mechanistic interest in the reactions of heterocycles with borane results from several recent papers[1], due to the fact that in this way regiospecific reductions of some heterocyclic systems could be achieved[1d,f,g] and sometimes a high stereospecificity of the reaction was also found[1b,d,i].

In this paper we describe the behaviour towards borane of 3-methylisoxazolo-[4,5-c]pyridines, whose synthesis[2a], photochemical rearrangements[2b] and nucleophilic substitution reactions[2c] we previously reported.

Protonation and quaternization with methyl fluorosulphonate of 3-methylisoxazolo[4,5-c]pyridine 1 was first carried out, in order to locate the point of attack of electrophilic reagents on this system. A comparison of ^{1}H-n.m.r. spectra of compound 1 in DMSO-d_6 alone or in the presence of D_2SO_4 (table) suggests that protonation of pyridine nitrogen atom occurs, since the downfield shifts of all signals are more evident for the pyridine protons. Quaternization of compound 1 with methyl fluorosulphonate confirmed this hypothesis. In fact the ^{1}H-n.m.r. spectrum of the resulting salt 2 shows (table) a very similar trend to that of protonated isoxazolopyridine 1, as a consequence of an electrophilic attack on the pyridine ring. Further evidence for this assignment was obtained by catalytic hydrogenation of fluorosulphonate 2, affording 1-methyl-4(1H)-pyridone 3, whose structure is in agreement with i.r. and n.m.r. spectra[3].



Treatment of isoxazolopyridine 1 with BH_3:THF gave different results according to molar ratio reagent:substrate. When 1 mMol of BH_3:THF was added to a solution of 1 (1 mMol) in cyclohexane (12 ml), the 1:1 borane-isoxazolopyridine adduct 4 (15%) was collected by filtration after 24 hours. Evaporation of the mother liquors and sublimation in vacuo of the residue afforded starting material (50%). Acidification followed by alkalinization of the unsublimed residue yielded the tetrahydroisoxazolopyridine 5, which was separated and characterized as its N-benzoyl derivative 10[3] (30%). The structure of adduct 4 follows from its spectroscopic data[3]; in particular, comparison of the ^{1}H-n.m.r. spectra of 4 and 2 led us to assign the position of the BH_3 group (table).

Table - ^{1}H-n.m.r. of compounds 1, 2 and 4

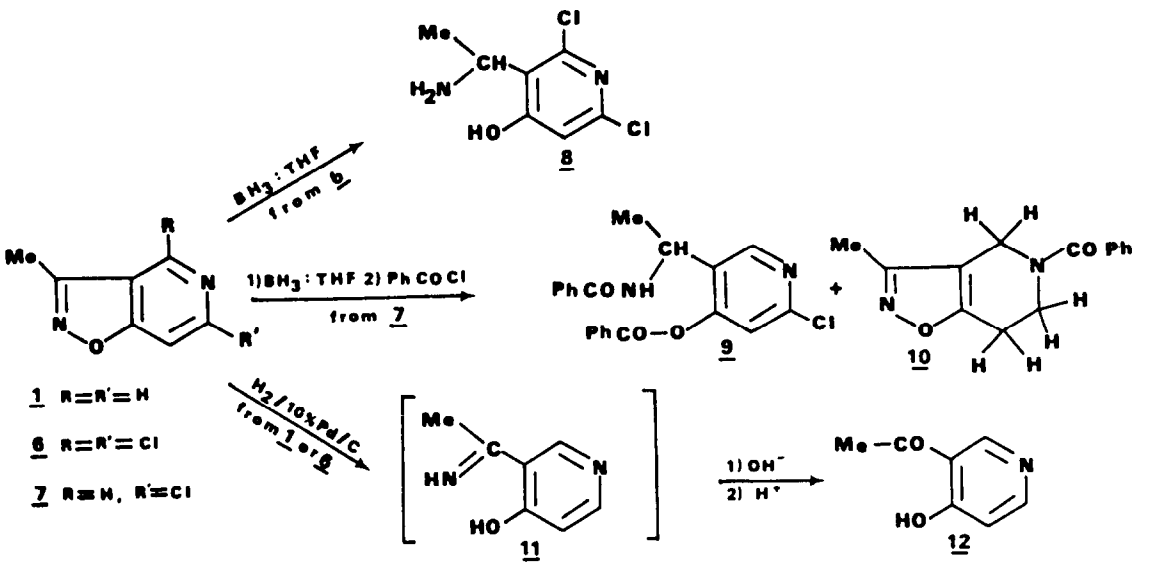
Compound	Solvent	H-4	H-6	H-7	Me
1	A	9.23	8.73	7.80	2.68
	B	9.03	8.67	7.49	2.68
	C	9.73	9.00	8.36	2.77
2	A	9.99	9.11	8.52	2.77
4	A	9.39	8.67	8.07	2.70
	B	9.13	8.66	7.68	2.68

A) DMSO-d_6; B) $CDCl_3$; C) DMSO-d_6 + D_2SO_4 (2 eqs)

The complex 4 is very stable: it was sublimed in vacuo and stored whithout decomposition at room temperature for many months; water and chloroform did not affect it whereas in DMSO solution it gave slowly the starting material 1 (half-

life 6 days at 22-24°). The transformation of 4 into the tetrahydroisoxazolopyridine 5 was achieved by reaction with BH_3:THF. As a consequence, when the isoxazolopyridine 1 was treated with an excess of borane, only compound 5 was obtained.

A different behaviour was found in the case of 4,6-dichloroisoxazolopyridine 6. Protonation of the pyridine system was not evidenced by ^{1}H-n.m.r. spectroscopy and borane treatment afforded 3-(1-aminoethyl)-2,6-dichloro-4-hydroxypyridine 8 [3] in good yield.



This results shows that borane attacks only the isoxazole nucleus if two substituents are present in the 4 and 6 positions of the pyridine ring. In fact, the monochloro derivative 7 reacted with borane to give a mixture of 9 [3] and 10, which were derived from the attack of reducing agent on the isoxazole and pyridine moieties, respectively.

The above reactions are of some synthetic value since, although in every case catalytic hydrogenation of the title compounds afforded only the ketone 12 [3], when the reduction is carried out by diborane, selective attack on the isoxazole or the pyridine ring can be achieved, depending on the substituents.

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) Compound 3: m.p. 132-134° (benzene), ν (KBr) 3180 (OH) and 1650 (CO) cm^{-1}; δ ($CDCl_3$) 1.45 (d, J 7.2, Me), 3.69 (s, NMe), 3.71 (exch. br. s, OH), 4.85 (q, J 7.2, CH), 6.34 (dd, $J_{5,6}$ 5.4, $J_{5,2}$ 2.0, 5H) and 7.27 (m, 2 and 6H). Compound 4: m.p. 116-118° (decomp.) (sublimation in vacuo); ν (KBr) 3100, 3070, 3045 (CH) and 2375, 2320, 2270 (BH_3) cm^{-1}. Compound 8: m.p. 219° (decomp.) (water); ν (KBr) 3200-2100 (NH_3^+) cm^{-1}; δ (DMSO-d_6) 1.42 (d, J 6.8, Me), 4.43 (q, J 6.8, CH), 6.09 (s, 5H) and 8.40 (exch. br. s, NH_3^+). Compound 9: m.p. 178-180° (ethanol); ν (KBr) 3320 (NH), 1740 and 1630 (CO) cm^{-1}; δ (DMSO-d_6) 1.56 (d, J 7.0, Me), 5.42 (m, q with D^+ in D_2O, CH), 7.35-7.97, 8.10-8.26 (m, 2 C_6H_5 and 5H), 8.67 (s, 2H) and 8.90 (d, J 7.0, exch. with D^+ in D_2O, NH). Compound 10: m.p. 113-114° (sublimation in vacuo); ν (KBr) 2960, 2920, 2900, 2870, 2850 (CH_2 and Me) and 1660 (CO) cm^{-1}; δ ($CDCl_3$) 2.21 (s, Me), 2.82 (t, J 6.0, 7 CH_2), 3.80 (t, J 6.0, 6 CH_2), 4.47 (s, 4 CH_2) and 7.44 (s, C_6H_5). Compound 12: m.p. 173-174° (decomp.) (sublimation in vacuo); ν (KBr) 3500-2600 (OH and H_2O) and 1670 (CO) cm^{-1}; δ (DMSO-d_6) 2.56 (s, Me), 6.37 (d, J 6.1, 5H), 7.71 (d, J 6.1, 6H), 8.19 (s, 2H) and 9.17 (exch. br. s, OH). Satisfactory elemental analyses were obtained for all new compounds. Synthetic details will be given in our full publication.

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