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NUCLEOPHILIC VERSUS ELECTROPHILIC PROPERTIES OF THE NITROGEN ATOM IN O-SULFONYL-HYDROXYLAMINE DERIVATIVES

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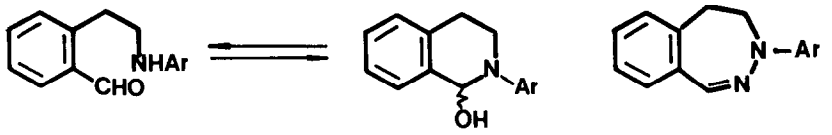
A recent publication by Suwinski, pertaining to the ambivalent character of hydroxylamine-O-sulfonic acid,[1] prompts us to publish our own results along these lines with the following reagents: hydroxylamine-O-sulfonic acid (HAS) and mesitylsulfonylhydroxylamine (MSH).

Tamura and his coworkers have made extensive use of MSH.[2] They showed in particular that δ-aminoaldehydes of type 1, which are in equilibrium with the corresponding pseudobases 2, lead in moderate yields to the corresponding benzodihydrodiazepines 3.[3] According to these authors the first step in these syntheses is an electrophilic attack of MSH upon the nitrogen atom of 1 leading to the N-amino intermediates 4, although these hypothetical intermediates have never been isolated.[2,5] An intramolecular condensation between the aldehyde and the NH_2 group of 4 was supposed to give in a second step the isolated benzodihydrodiazepines 3.



1 2 3

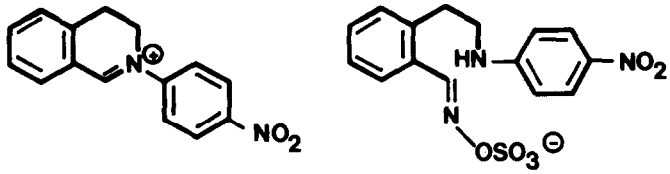
a) Ar=C_6H_5; b) Ar=p-C_6H_4-Cl; c) Ar=p-$C_6H_4NO_2$; d) Ar=o-$C_6H_4NO_2$

We have reacted both MSH and HAS with 1⇌2 and our observations do not agree with Tamura's hypothesis. Our results, indicated below, clearly, point to a nucleophilic attack of MSH or HAS upon 1⇌2 during the very first step of the reaction.

4 5

i) A suspension of 1c⇌2c in a HAS-water solution was vigorously stirred at room temperature and gave after a few minutes a red salt. Elemental analyses and ^{1}H and ^{13}C NMR spectral data are consistent with structure 6 which we assign to this salt (the detailed NMR spectral analyses will be published in the final paper. Let us mention that the ^{13}C NMR spectrum of the cationic moiety of 6 is superimposable with the same cation which has been synthesized separately)

ii) Heating salt 6 in water at about 80° leads to its decomposition. Besides the expected nitrile 5c (40%), one obtains also small amounts of the corresponding diazepine 3c (4%). These two products obviously originate from the anion 6A. The main product (43%) is the pseudo-base 2c which derives from the cationic part 6C.



6C 6A

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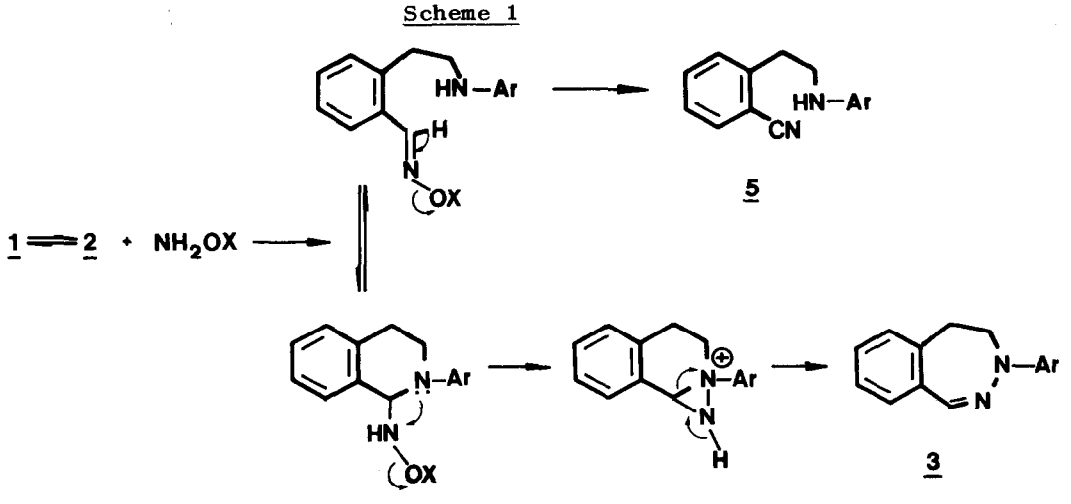
iii) Although the oxime - which we postulate as an intermediate by analogy with anion 6A - could not be isolated when 1c⇌2c are reacted with MSH, we do get the O-[2,4-dinitrophenyl]oxime of 1c with O[2,4-dinitrophenyl]-hydroxylamine. Heating this oxime leads to nitrile 5c in 60% yield and to small amounts of diazepine 3c.

In order to account for these experimental facts we propose the following mechanistic scheme (Scheme 1)

Scheme 1

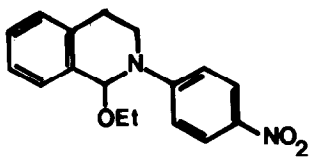


By analogy with results found by us[6,7] and by others[2,8,9] it was tempting to postulate a nucleophilic attack of HAS or MSH upon the carbonyl group of 1 during the first mechanistic step. However, we actually favour a nucleophilic attack upon C-1 of the pseudobase 2 or of the dihydroisoquinolinium cation, for the following reasons:

i) IR and ^{1}H and ^{13}C NMR spectra clearly show that the p-nitro starting material appears in solution almost entirely in its pseudo-base form 2c. On the contrary the o-nitro isomer, in the same conditions, appears in its δ-amino-aldehyde form 1d. The p-nitro starting material (ring-closed tautomer 2c predominant if not exclusive) reacts much faster with MSH than the o-nitro starting material which is mostly in its ring-opened form 1d. A competition experiment, starting from 1 equivalent of 1d, 1 equivalent of 2c and 0.9 equivalent of HAS, leads to diazepine 3c and to nitrile 5c as the major reaction products. Only trace amounts of diazepine 3d and of nitrile 5d could be detected.

ii) Reaction of an anhydrous solution of MSH with the aminal 7 leads instantaneously to the corresponding diazepine 3c and nitrile 5c.

iii) Reaction of the dihydroisoquinolinium perchlorate 8 in an anhydrous CH_2Cl_2/CH_3CN solution with MSH leads at room temperature to the same products 3c and 5c



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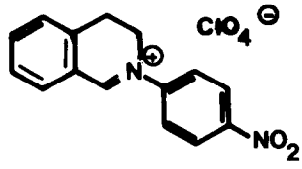

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The net result of the first reaction step is the formation of a carbon-nitrogen bond. We believe that an equilibrium is obtained as indicated in scheme 1. By analogy with known examples[6,7,10] elimination of H_2SO_4 or of the arylsulfonic acid respectively yields the corresponding nitriles 5. The ring closed form could lead in two steps to the corresponding diazepines (Scheme 1), a proposal for which there are many analogies in the literature.[1,11,14]

Nucleophilicity of the nitrogen atom belonging to the aniline function plays a significant role in the second step of the diazepine formation. As can be seen from Table 1 the yield of diazepine decreases when lowering the nucleophilicity, whether HAS or MSH is used (the pKa's of the corresponding anilines are a good measure of the relative nucleophilicity). Simultaneously the yields of nitrile formation increase.

Table 1 Yields of diazepines 3 and of nitriles 5 as a function of the relative nucléophilicities of the aniline nitrogen atoms

Ar of 1 2	Diazepines 3		Nitriles 5		pKa of Ar-NH_2
	HAS	MSH	HAS	MSH	
C_6H_5	14%	76%	45%	17%	4,63
p Cl C_6H_4	12%	70%	51%	22%	4,15
p NO_2-C_6H_4	7%	45%	70%	50%	1,0
o NO_2 C_6H_4	traces	20%	75%	77%	1

It should be noted that nitriles, the formation of which has been overlooked by Tamura,[3] always occur along with the corresponding diazepines, whether MSH or HAS is used (Table 1)

From all these experimental results we conclude that MSH and HAS have a similar reactivity spectrum with compounds $1 \rightleftharpoons 2$; although the former gives diazepines in better yields. Furthermore these hydroxylamine derivatives react as nucleophilic entities during the first step. The electrophilicity of the sulfonylated nitrogen atom plays a role in the second reaction step, and only for the formation of the diazepines.

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