Solvent-Dependent Competitive Rearrangements of Cyclic Tertiary Propargylamine *N*-Oxides

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In protic media, cyclic propargylamine *N*-oxides **1** undergo solvent-dependent competitive rearrangements leading to enamino aldehydes **5**, acrylamides **3**, and secondary amines **4**. The ratios of the products are evaluated and the possible mechanism of the competing reactions is interpreted by reaction kinetics studies and ab initio calculations.

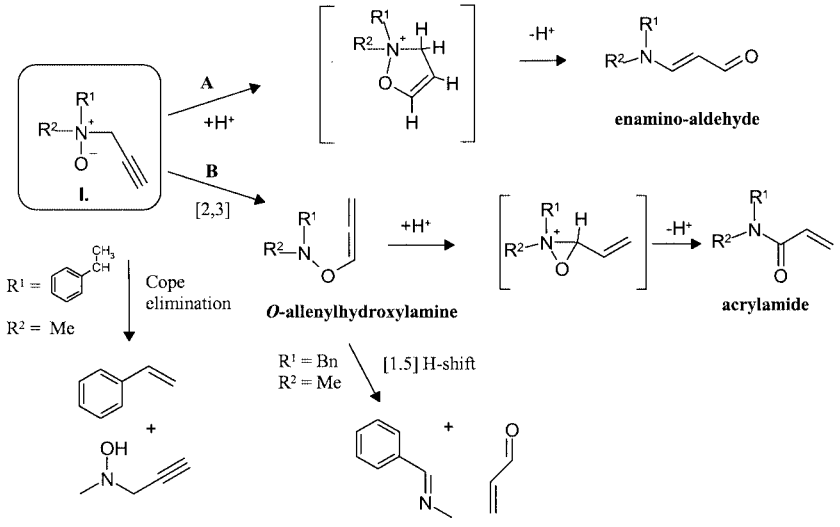
Introduction

Certain propargyl-substituted tertiary amines are irreversible monoamine-oxidase (MAO) inhibitors.[1] One major metabolic degradation path of tertiary amines starts with the oxidation of the tertiary nitrogen atom.[2] This can be followed by enzymatic and chemical transformations.[3] The chemistry of propargylamine *N*-oxides in protic media is little known. It was our aim to study these transformations.

The Meisenheimer[2,3] sigmatropic rearrangement[4] of tertiary propargylamine *N*-oxides **I** in aprotic media to give *O*-allenylhydroxylamines has been described for cyclic derivatives[5] and benzylamine derivatives (e.g. pargylin).[6] The *O*-allenylhydroxylamine product of the benzylamine derivative is known to undergo a further sigmatropic [1,5]-H shift rearrangement[6] (Scheme 1).

N-Oxides having a hydrogen atom in a position that is β to the nitrogen atom may undergo the characteristic Cope elimination.[7]

We recently described a novel rearrangement of pargylin *N*-oxide (**I**: R^1 = Bn; R^2 = Me) in protic medium, leading to a new enamino aldehyde with the appearance of the secondary amine and a new acrylamide-type product in the reaction mixture.[8] We suggested possible mechanisms for these transformations: the enamino aldehyde major product



Scheme 1. Possible rearrangements of tertiary propargylamine *N*-oxides

is formed by an ionic mechanism through an isoxazolinium-type intermediate state (route A), while the acrylamide by-product results from the Meisenheimer rearrangement

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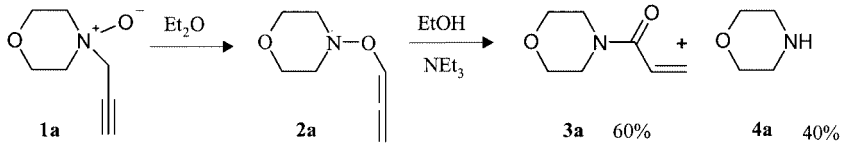
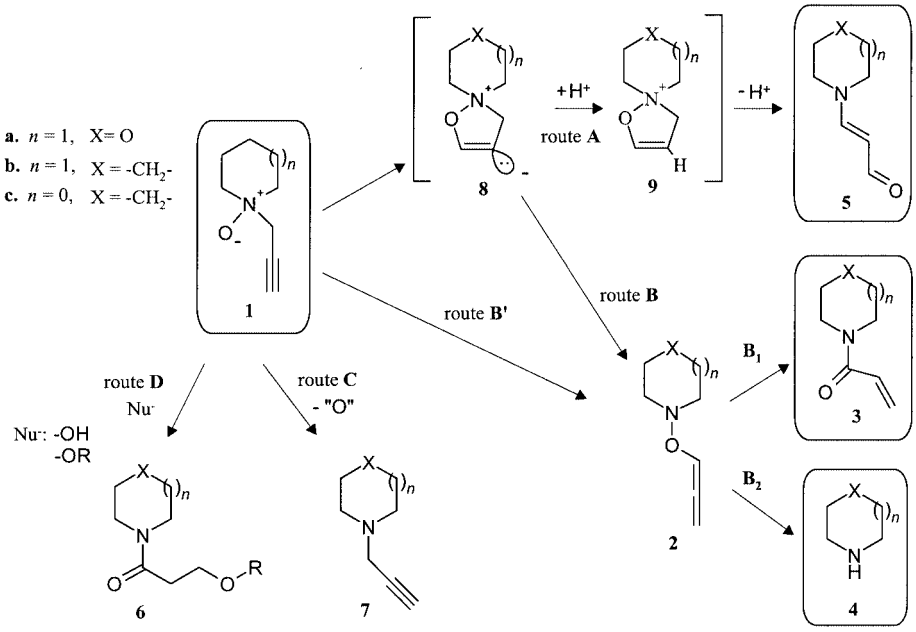
(route B) by further transformation of the primarily formed *O*-allenylhydroxylamine.

We have now extended these transformations to cyclic propargylamine *N*-oxides where R^1 and R^2 form a 5- or 6-membered ring, i.e. morpholine, piperidine, and pyrrolidine derivatives **1a**, **1b**, and **1c**. The aim was to exclude the Cope elimination, which is sterically hindered in these structures.[9] Further transformation of the *O*-allenylhydroxylamine Meisenheimer product by a [1,5]-H shift is also excluded in these structures because of the absence of suitable protons. Evidence from preparative experiments was sought for the route of formation of the secondary amine and acry-



Scheme 2



Scheme 3. Competing reaction routes of cyclic tertiary propargylamine *N*-oxides

Table 1. Distribution of the products obtained from *N*-oxide **1a** and rate constants calculated for route A at 65 °C in alcohols with different acities

Solvent	Anion/cation-solvating ability		Rate constant 10^4 k [s^{-1}]	Product [mol %], route				
	Acity	Basity		**5a**, A	**3a**,B_1	**4a**,B_2	**7a**,C	Others
MeOH	0.75	0.50	0.78	33	11	29	6	21
EtOH	0.66	0.45	1.14	47	14	17	5	17
*n*PrOH	0.63	0.44	1.47	42	14	15	8	21
*i*PrOH	0.59	0.44	2.16	57	11	13	14	5
*t*BuOH	0.45	0.50	3.31	69	8	11	8	4

Table 2. Distribution of the products from **1a** in *t*BuOH at different temperatures and activation parameters calculated for route A

T [°C]	Rate constant 10^4 k [s^{-1}]	$\Delta H^{\#}$ [kJ/mol]	$\Delta S^{\#}$ [J/molK]	Products [mol %], route				
				5a, A	**3a**, B_1	**4a**, B_2	**7a**, C	Others
50	0.60	98.62	−20.6	71	2	17	4	6
65	3.31			69	8	11	8	4
79	15.0			65	9	14	9	3

lamide byproducts. The effects of the reaction conditions on the rates of the competing rearrangements were studied. Reaction kinetics measurements were expected to yield information on the mechanism of the rearrangements. Experimental results were evaluated in the light of the ab initio calculations we recently performed on these reactions.

Results and Discussion

Kinetics Studies

The rearrangements of cyclic propargylamine *N*-oxides **1a**−**c** were effected in alcohols; the reactions were monitored by GC. The compositions of the mixtures were determined by using reference samples of the expected products (all are known compounds) synthesized independently. Final reaction mixtures contained the expected enamino aldehyde **5**, acrylamide **3**, and secondary amine **4** in all three cases, together with the corresponding tertiary (parent) amine **7** and byproducts. The *O*-allenylhydroxylamine **2** (the Meisenheimer rearrangement product) appeared as an intermediate.

A systematic study of the rearrangement was performed on the morpholino model **1a**.

To distinguish the rearrangement routes, we first prepared the *O*-allenylhydroxylamine Meisenheimer product in an aprotic medium (Et_2O) and investigated its further transformations in a protic medium. In ethanol, the *O*-allenylhydroxylamine **2a** gave exclusively the morpholine **4a** and the acrylamide **3a**. In response to base (triethylamine) addition, the amount of the acrylamide increased (Scheme 2). The base is thought to abstract a proton from the oxaziridine intermediate[8] (Scheme 1). These results led us to ascribe the acrylamide **3** and secondary amine **4** to the Meisenheimer route (B) for all three *N*-oxides **1a**−**c**.

Next, we investigated how the solvating abilities of the solvents affected the proportions of the Meisenheimer route (B) and our novel rearrangement route (A). Reactions of **1a** were carried out in a series of alcohols with significantly different anion-solvating abilities (acity), but similar cation-solvating abilities (basity).[10] The formation of enamino aldehyde **5** was followed [transformation of the starting compound **1** and the formation of **2** (route B) could not be followed because of the instability of these compounds under GC conditions]. Rates were clearly of first order and the rate constants were sensitive to the solvent (Table 1). With decreasing anion-solvating abilities of the solvent, the participation of route A and the rate of the reaction increased.

For the same model (**1a**), we determined the rate constant at three different temperatures in *tert*-butyl alcohol. From the temperature dependence of the rate constants, we calculated (according to Eyring[11]) the activation parameters, $\Delta H^{\#}$ and $\Delta S^{\#}$ of the formation of enamino aldehyde **5a** (Table 2).

The small negative entropy of activation indicates a considerable decrease in randomness in the activated complex, in agreement with our supposition that the rearrangement involves a cyclic (isoxazoline ring) transition state.

From $\Delta H^{\#}$ and $\Delta S^{\#}$ we have also calculated the free energy of activation ($\Delta G^{\#}$) for the reaction in *tert*-butyl alcohol at 65 °C (105.6 kJ/mol). From that value and the reaction rates in various alcohols at 65 °C, the $\Delta G^{\#}$ values of the reactions in various alcohols were calculated (see Table 3).

Table 3. $\Delta G^{\#}_{B} - \Delta G^{\#}_{A}$ and $\Delta G^{\#}_{AB}$ values determined for reactions performed in alcohols with different acities

Solvent	Acity	$\Delta G^{\#}_{AB}$ [kJ/mol]	ab initio	$\Delta G^{\#}_{B} - \Delta G^{\#}_{A}$ [kJ/mol]	ab initio
MeOH	0.75	109.7	107.1	−0.540	−14.400[a]
EtOH	0.66	108.6		1.169	
*n*PrOH	0.63	107.9		1.040	
*i*PrOH	0.59	106.8		2.430	
*t*BuOH	0.45	105.6		3.624	

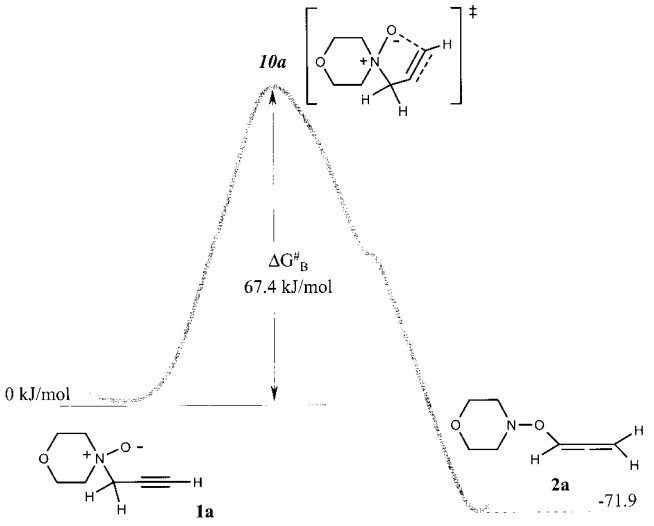
[a] The correlation between the experimental and theoretically calculated results is not sufficient and comes from the model containing only two molecules of MeOH.

Interpretation of the Results in the Light of Theoretical Calculations

The results obtained from preparative experiments and reaction kinetics measurements left several unanswered questions. For example, the question of whether the two competitive reactions (routes A and B) proceed through different transition states (TS) or pass through a common, rate-determining TS to a common intermediate from which different products may arise in subsequent fast steps (see Scheme 3) controlled by different experimental conditions. To understand the energetic difference between the competitive routes A and B, theoretical methods, HF, MP2 and DFT (B3LYP) were applied.[12] The mechanism of the reactions was studied on the morpholino model **3a**, in vacuo − mimicking the aprotic solvent with an isolated molecule − and in the presence of two molecules of solvent (MeOH) − required for proton transfer and simulating protic media. Energy profiles based on these ab initio calculations are presented in Schemes 4 and 5.

In the aprotic medium model (Scheme 4), starting from the *gauche* conformation of **1a**, the O1 and C5 atoms approach each other and the forthcoming reaction passes through only one TS (***10a***: $\Delta G^{\#} = +67.4$ kJ/mol, $\Delta S^{\#} = -15.9$ J/molK), which leads to only one final product, the *O*-allenylhydroxylamine derivative **2a** (route B′) (Scheme 3). We emphasise that under aprotic conditions the Meisenheimer rearrangement does not involve any intermediate; it has a real [2,3] sigmatropic mechanism, in agreement with the literature.

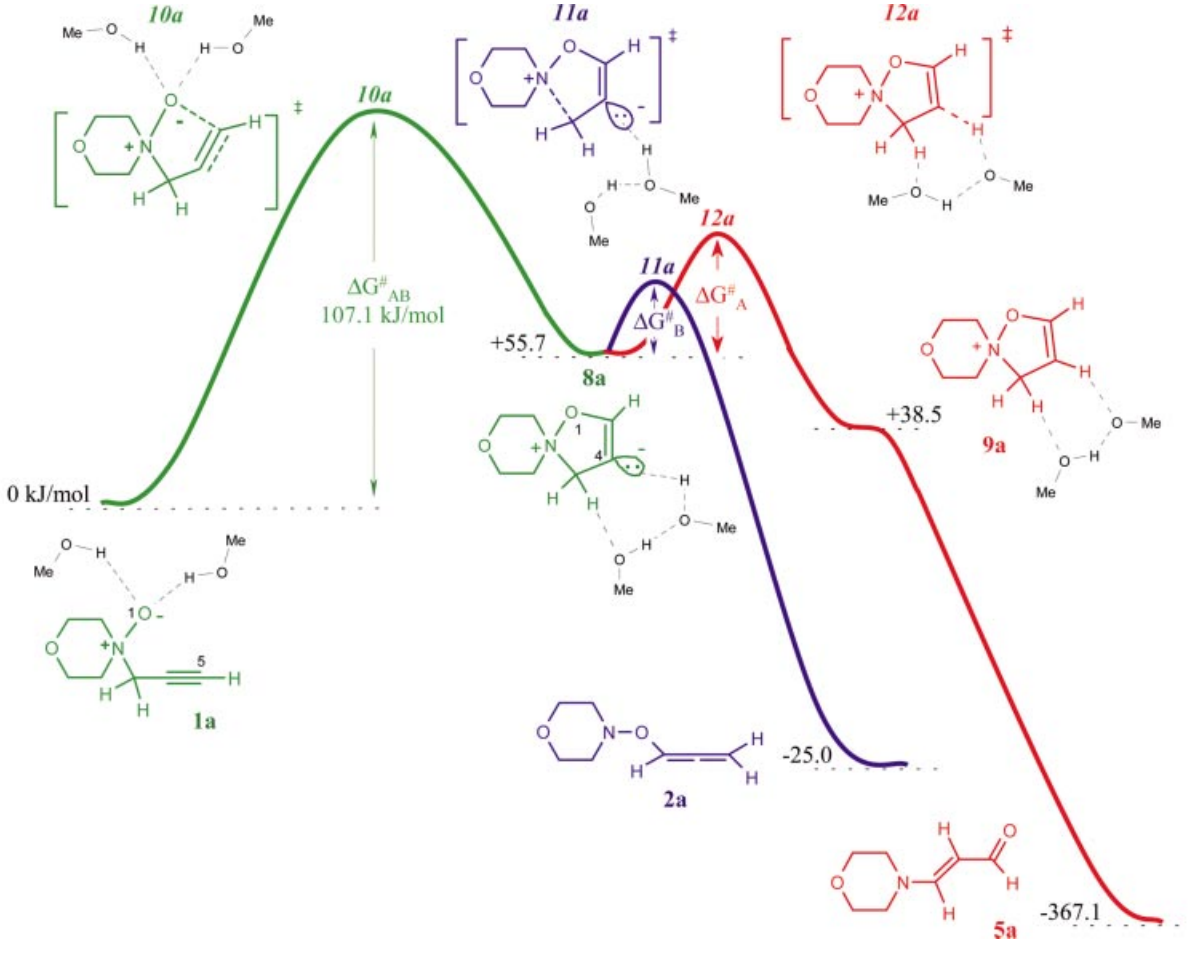
In the protic medium model, on the contrary, we have found that a hydrogen bond stabilized the isoxazoliniumtype zwitterionic intermediate (see **8a** in Scheme 5) for both transformations with the same TS (***10a***: $\Delta G^{\#}_{AB} = +107.1$ kJ/



Scheme 4. Energy profile of route B′ in aprotic medium, based on ab initio calculations

mol). In the stable intermediate−solvent complex ***11a*** the first MeOH molecule forms a strong (1.80 Å) hydrogen bond with the nonbonding electron pair of the negatively charged C4 atom, and the second MeOH molecule is linked to the first one. A very weak hydrogen bond (2.4 Å) is observed between the H3 atom and the oxygen atom of the second MeOH molecule.

For the stable intermediate **8a**, two reaction routes are open: without protonation it can follow route B, giving **2a** through TS ***11a*** (calcd. $\Delta G^{\#}$ = 2.2 kJ/mol); or it follows route A, giving **5a**. Route A can be realized by protonation of the C4 atom of **8a** by the first MeOH molecule, through TS (***12a***) (calcd. $\Delta G^{\#}$ = 16.6 kJ/mol). An unstable protonated intermediate **9a** was recognized during the protonation reaction which, after proton abstraction, gives the final enamino aldehyde product **5a**. In a protic medium, according to the ab initio calculations, the rate-determining step of the reaction sequence is the cyclisation of the *N*-oxide **1a** to give the zwitterionic isoxazolinium intermediate **8a**. Consequently, the activation parameters determined by us in the reaction kinetics measurements for route A, apply to the TS involved in the formation of the common intermediate (**8a** in this model). The free energy of activation ($\Delta G^{\#}_{AB}$) determined for the methanolic reaction by kinetics measurements and obtained by ab initio calculations using the model with two molecules of MeOH are in very good agreement (see Table 3). In this suggested mechanism, the ratio of the products arising from routes A and B is finally determined by the ratio of the fast parallel reactions of



Scheme 5. Energy profile of the competing reactions in protic medium based on ab initio calculations

routes A and B, proceeding from this common intermediate **8a**.

Discussion of the Solvent Dependence of the Competing Reactions

From the ratio of products arising from routes A and B at a given temperature (Table 1) we determined the difference between the free energies of activation ($\Delta G^{\#}_{B} - \Delta G^{\#}_{A}$) of the competing routes in various alcohols at 65 °C, and the free energy of activation ($\Delta G^{\#}_{AB}$) of the rate-determining step of these reactions (Table 3). Results indicate significant solvent dependence not only in reaction rates, but also in the product distribution.

In Scheme 6, using a schematic energy level diagram, we explain the above solvent dependencies, illustrating the energy levels of the starting and transition states in methanol and in *tert*-butyl alcohol.

In the rate-determining step (ring closure of the *N*-oxide **1a** to TS ***10a***), the difference in the energy levels of the starting state in methanol and in *tert*-butyl alcohol must be larger than that in the transition state, where the hydrogen bonds are weaker. This may explain the acceleration of the reaction when changing the solvent from methanol to *tert*-butyl alcohol.

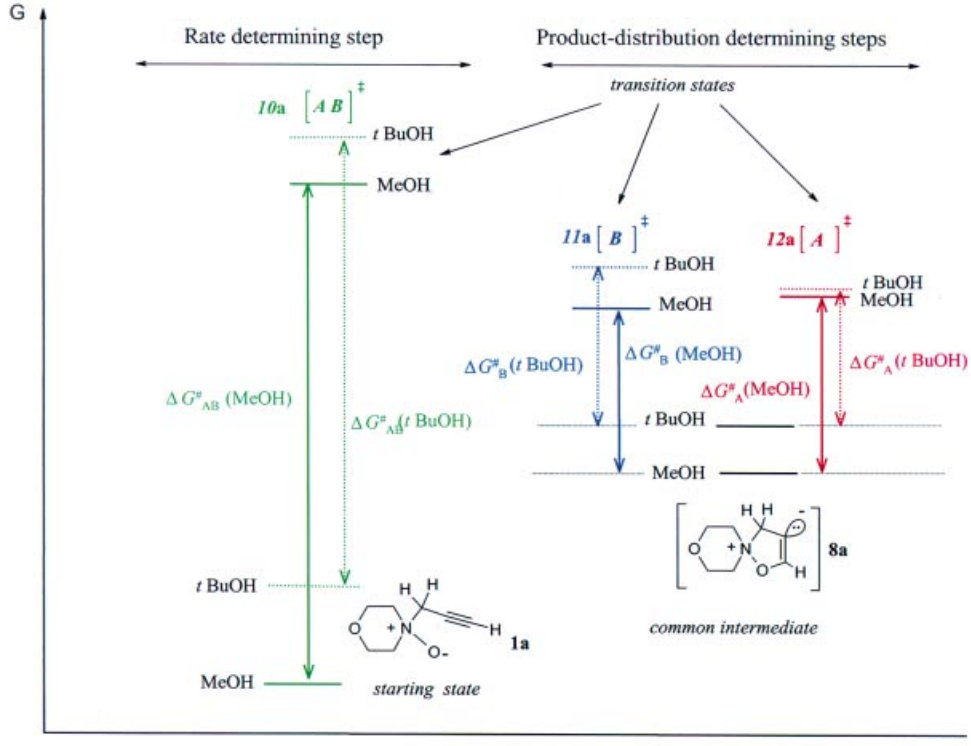
In the product-distribution step, the value of $\Delta G^{\#}_{B} - \Delta G^{\#}_{A}$ increases with decreasing anion-solvating ability (acity) of the alcohol (see Table 3). The free energy of activation of **8a** to TS ***12a*** ($\Delta G^{\#}_{A}$), which leads to the enamino aldehyde (route A), seems to be more dependent on the acity of the solvent than is $\Delta G^{\#}_{B}$, leading to the Meisenheimer product (route B). These results can be interpreted in terms that the transition state of route A (***12a***) approaches a protonated isoxazoline structure which no longer has an anionic character; thus, a change in the anion-solvating ability of the alcohol has less effect on the energy levels of TS ***12a*** than on the common zwitterionic intermediate **8a**, contrary the route B, where protonation does not occur.

The study of *N*-oxides **1b** and **1c** in ethanol and *tert*-butyl alcohol revealed a similar effect of the solvent on the product distribution as for **1a** (Table 4).

Table 4. Product distribution in the rearrangements of **1a**–**c**

N-Oxide	Solvent	Temp. [°C]	Products [mol %], route **5**, A	**3**, B_1	**4**, B_2	**7**, C	Others
1a	EtOH	79	48	13	14	5	20
	*t*BuOH	65	69	8	11	8	4
1b	EtOH	79	35	25	13	4	23
	*t*BuOH	65	61	14	14	9	2
1c	EtOH	79	44	17	25	3	11
	*t*BuOH	65	74	4	16	3	3

The results in Tables 3 and 4 support experimentally the structures estimated by ab initio calculations for the common intermediate **8** and for the transition states ***10***, ***11***, ***12*** involved in the rate-determining and product distribution determining steps of the rearrangements.



Scheme 6. Schematic energy level diagram: solvent dependence of the rate-determining step and of the product distribution determining steps of the rearrangements

Effect of Bases

The role of the base in these transformations was investigated on the morpholino model **1a**. We found that a non-nucleophilic base shifted the ratio of the two transformations towards the Meisenheimer route and, within this, towards acrylamide formation (Table 5, Entries 2, 3). A small amount of acid (e.g. 0.2 equiv. HCl) exerted the opposite effect (Entry 4).

Table 5. Effect of the base on the rearrangement of **1a** (79 °C)

Entry	Reaction medium	Product [mol %], route				
5a, A	**3a**, B_1	**4a**, B_2	**7a**, C	Others		
1	EtOH	48	13	14	5	20
2	EtOH +0.2 equiv. NEt_3	25	24	16	12	23
3	EtOH +1 equiv. NEt_3	12	42	21	14	11
4	EtOH +0.2 equiv. HCl	63	2	14	3	18
5	EtOH +0.2 equiv. NaOEt	1	6	3	0	90

The above results support our assumption: the negative effect of bases (and the positive effect of acids) can be explained by the protonation step required to produce the isoxazolinium cation intermediate. If this protonation is slowed down, less isoxazolinium (and less enamino aldehyde) is formed; if it is promoted (by acid), the opposite is the case.

Rearrangements depend on the negatively charged oxygen atom of the *N*-oxide to attack the triple bond as a nucleophile; thus, the *N*-oxide hydrochloride salts (**1**·HCl) remain intact in alcoholic solution.[8] Excess of a nucleophilic base forces both rearrangements back drastically and brings about other reactions (Entry 5) not discussed here. Among others, product **6** was identified by GC-MS. The acrylamide **5** under similar conditions did not furnish **6**.

Results obtained for the six-membered ring models **1a** and **1b** (see Table 4) can also be explained by the effect of bases: from **1b** more acrylamide **3b** is formed than from **1a**, because of the more basic reaction medium, due to the more basic character of the piperidine derivatives.

We investigated the transformation of *N*-oxides **1a**−**c** in aqueous buffered media at pH = 7 and 11. Only the formation of the UV-active enamino aldehyde **5** and acrylamide **3** was followed by HPLC (Table 6).

Table 6. Enamino aldehyde **5** and acrylamide **3** formed from *N*-oxides **1a**−**c** as a function of the pH

N-Oxide		pH = 7		pH = 11	
		5	**3**	**5**	**3**
Morpholine	**1a**	59	0	15	8
Piperidine	**1b**	51	0	12	8
Pyrrolidine	**1c**	48	0	23	4

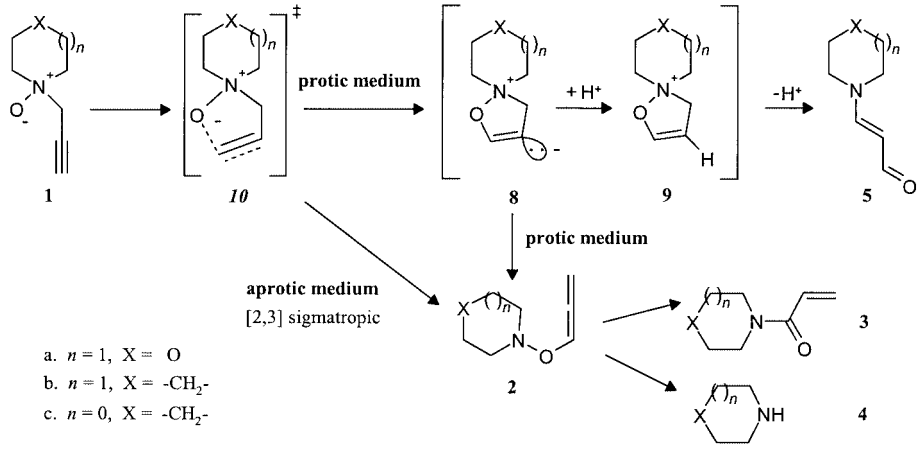
The ratio of the enamino aldehyde decreased with increasing pH, which can be ascribed to its hydrolysis at a higher pH. The acrylamide was not detected in pH = 7 buffer, whereas it did appear at pH = 11. This is in agreement with the results obtained in ethanol with triethylamine (Table 5), where the base helped the formation of acrylamide **3a**.

Unlike the alcohol solutions, in aqueous buffered media there are little differences between the results obtained for the six-membered models **1a** and **1b**.

Beside rearrangement routes A and B, the loss of oxygen (route C) also occurred, to various degrees, in the transformation of the *N*-oxides, yielding the tertiary amine **7**. Route C is more pronounced in the presence of triethylamine and in isopropyl alcohol, probably due to the oxidizability of these materials.

Conclusion

The present results indicate that the recently revealed[8] rearrangement of propargylamine *N*-oxides **I** (R^1 = Bn; R^2 = Me), leading to enamino aldehyde (route A), is a significant transformation path, also for cyclic propargylamine *N*-oxides **1a**−**c** exclusively in protic media.[8] Thus, the scope of this rearrangement can be extended to *N*-oxides **I** where R^1 and R^2 form a morpholine, piperidine or pyrrolidine ring (Scheme 1).



Scheme 7

The mechanism of the Meisenheimer rearrangement is different in protic and aprotic medium. In an aprotic medium, the [2,3] sigmatropic mechanism (route B′) is probable, while in a protic medium, according to ab initio studies, both routes A and B pass through a common isoxazolinium-type intermediate **8** formed in the rate-determining step. This common intermediate may transform, in the product ratio determining steps, into the *O*-allenylhydroxylamine Meisenheimer product **2** or the enamino aldehyde product **5** (Scheme 7). In further transformations, the Meisenheimer product **2** partly degrades into the secondary amine **4** and partly rearranges into the acrylamide **3**.

Reaction kinetics measurements in alcohols with different anion-dissolving abilities, in agreement with ab initio studies, afforded information on the structure of the transition state involved in the rate-determining step and on those involved in the product distribution determining steps of the competing routes, supporting our assumption on the mechanism of these reactions.

Experimental Section

General: Compounds **1a** and **2a** were prepared according to literature procedures without any significant modification.[5a] Compounds **7a**−**b**[13] and **7c**[14] were obtained by propargylation of **4a**−**c**, compounds **5a**,[15] **5b**,[16] **5c**[17] by Michael addition of **4a**−**c** to propargyl aldehyde, compounds **3a**,[18] **3b**,[19] **3c**[20] by acylation of **4a**−**c** by acryloyl chloride. All other reagents and solvents were used as obtained from commercial sources without further purification. Melting points were determined with a Büchi 535 apparatus and are uncorrected. IR spectra were recorded with a Bruker IFS-28 instrument. Elemental analyses were performed with a Carlo Erba Mod 1106 Analyser. NMR spectra were recorded with a Bruker DRX-400 spectrometer operating at 400 MHz; chemical shifts (δ) are given in ppm and were measured with reference to residual solvent peaks. Gas-phase chromatograms of the rearrangement reaction mixtures were recorded with an HP-6890 chromatograph equipped with a flame ionization detector under the following conditions: RTX-1301 capillary column, helium as the vector gas (initial flow: 0.6 mL/min), temperature of injector 250 °C and detector 280 °C, temperature of the oven: isothermal 100 °C for 15 min, then 100−250 °C (10 °C/min), then 250 °C for 30 min. HPLC analyses were performed with a Waters Alliance 2690 chromatograph equipped with a 996 PDA detector, column: μBonda-Pak C18 10μm, mobile phase: 100 mM $(NH_4)_3$-phosphate/acetonitrile (8:2) pH = 7.5, flow rate: 1.0 mL/min.

***N*-Oxide Hydrochloride Salts 1a−c:** To a stirred solution of **7a**−**c** (20 mmol) in chloroform (10 mL) 3-chloroperbenzoic acid (7.6 g, 55 mmol) in chloroform (50 mL) was added dropwise at 0−5 °C over a period of 30 min. After 2 h of stirring below 5 °C, a saturated hydrogen chloride solution in diethyl ether (10 mL) was added dropwise and the reaction mixture was stirred for 1 h. The precipitated 3-chlorobenzoic acid was filtered off, the filtrate was concentrated to dryness in vacuo at 30 °C. The oily residue was triturated with diethyl ether (50 mL + 2 × 30 mL). The crystalline product was filtered off, washed with diethyl ether, and recrystallised from ethanol.

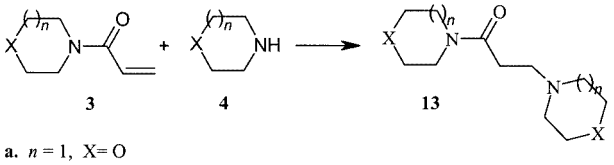
1a: White powder, 86% yield, m.p. 138−139 °C. IR (KBr): $\tilde{\nu}$ = 2128 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 3.82 (m, 4 H), 3.95 (m, 4 H), 4.04 (t, *J* = 2.4 Hz, 1 H), 4.93 (d, *J* = 2.4 Hz, 2 H), 13.0 (1 H) ppm. $C_7H_{11}NO_2$·HCl (177.63): calcd. C 47.33, H 6.81, N 7.89, Cl 19.96; found C 47.42, H 6.82, N 7.81, Cl 20.05.

1b: White powder, 75% yield, m.p. 150−151 °C. IR (KBr): $\tilde{\nu}$ = 2124 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 1.36−1.64 (m, 2 H), 1.79−1.92 (m, 4 H), 3.66−3.83 (m, 4 H), 4.01 (t, *J* = 2.4 Hz, 1 H), 4.81 (d, *J* = 2.4 Hz, 2 H), 12.6 (1 H) ppm. $C_8H_{13}NO$·HCl (175.66): calcd. C 54.70, H 8.03, N 7.97, Cl 20.18; found C 54.62, H 7.92, N 7.96, Cl 20.25.

1c: White powder, 72% yield, m.p. 98−99 °C. IR (KBr): $\tilde{\nu}$ = 2129 cm^{-1}. ^1H NMR ([D$_6$]DMSO): δ = 2.12 (m, 4 H), 3.81−3.96 (m, 4 H), 3.76 (t, *J* = 2.8 Hz, 1 H), 4.89 (d, *J* = 2.8 Hz, 2 H), 12.7 (1 H) ppm. $C_7H_{11}NO$·HCl (161.63) calcd. C 52.02, H 7.48, N 8.67, Cl 21.93; found C 49.95, H 7.59, N, 8.60, Cl 22.06.

Transformation of the *O*-Allenylhydroxylamine 2a in Alcoholic Medium: The *O*-allenylhydroxylamine **2a** (2 mmol) was refluxed for 1 h in ethanol (10 mL) containing NEt_3 (2 mmol). The composition of the reaction mixture was determined by GC.

General Procedure for the Rearrangement of the *N*-Oxides 1a−c in Alcoholic Media: The hydrochloride salt of the *N*-oxide **1a**−**c** (1 mmol) was dissolved/suspended in the appropriate alcohol (10 mL). The *N*-oxide base was liberated by the addition of 1 mmol of NaOEt. The reaction mixture was stirred at the given temperature until the *N*-oxide was completely transformed (as followed by TLC). Experiments investigating the effect of the base (Table 5): Base **1a** (1 mmol) was refluxed in ethanol (10 mL) in the presence of the appropriate amount of NEt_3 or NaOEt, except for Entry 4 of Table 5, where 1 mmol of **1a**·HCl was made to react in the presence of 0.8 mmol of NaOEt. The compositions of the reaction mixtures were determined by GC (Scheme 8, Table 7). The amounts of the acrylamide **3** and secondary amine **4** have been corrected in each case with the amount of the Michael adduct **13** formed from them; see Tables 1−5.



a. *n* = 1, X = O
b. *n* = 1, X = -CH_2-
c. *n* = 0, X = -CH_2-

Scheme 8

Crossover Procedures: The acrylamide **3a** (1 mmol) was dissolved in ethanol (10 mL) and refluxed for 3 h in the presence of NaOEt (1 mmol). No sign of the formation of **6** was detected by GC, indicating that **6** is not formed from **3a** by Michael addition. The acrylamide **3a** (1 mmol), dissolved in ethanol (10 mL), was refluxed for 3 h in the presence of morpholine (1 mmol). The formation of **13** was confirmed by GC. Conversion by GC: 64%.

General Procedure for the Rearrangements of the *N*-Oxides 1a−c in Aqueous Buffered Media: The hydrochloride salt of the *N*-oxide **1a**−**c** (1 mmol) was dissolved in 1 N NaOH solution (1 mL), then it was diluted to 20 mL with the appropriate buffer. The reaction mixture was stirred at 65 °C until the *N*-oxide had disappeared. The amounts of the enamino aldehyde **5a**−**c** and acrylamide **3a**−**c** products were determined by HPLC from the aqueous phase. The amount of the acrylamide was corrected with the amount of the

Table 7. GC retention times of the products

N-Oxide	Product/R_t [min]						
1	Products with reference standards				Products identified by GC-MS		
	4	**7**	**3**	**5**	**2**	**6**	**13**
a	12.5	22.0	29.2	35.6	26.6	29.5	46.7
b	10.1	20.6	29.3	36.3	26.2	28.8	44.3
c	7.9	16.9	28.8	35.0	24.7	27.5	40.0

Michael adduct **13a**−**c** as measured by GC from the chloroform extract of the cooled reaction mixture; see Table 6.

Reaction Kinetics Procedures: The hydrochloride salt of the *N*-oxide of **1a** (1 mmol) was dissolved/suspended in the solvent (10 mL) and the free *N*-oxide base was liberated in situ by 1 mmol of NaOEt. The reaction mixture was stirred at the given temperature (maintained constant within ±0.2 °C). The kinetics of the *N*-oxide rearrangement leading to the enamine aldehyde product **5a** was studied by monitoring the formation of **5a**, injecting the cooled samples from the reaction mixture into the GC. In all the cases, the value of A_∞ was determined experimentally for each run by leaving the reaction mixture at the specified temperature until there was no further change in the concentration of the enamino aldehyde product. All the kinetics runs were carried out to 90% completion. Rate constants were calculated from the slope of $\ln(A_\infty - A_t)$ vs. time. The error in k is less than 3% for all examined alcohols. The enthalpy of activation and the entropy of activation were calculated according to Eyring from the linear regression of log (k/T) (obtained from experiences in *tert*-butyl alcohol) vs. $1/T$ by the least-squares method.

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