Novel Intramolecular Rearrangement of Tertiary Propargylamine *N*-Oxides

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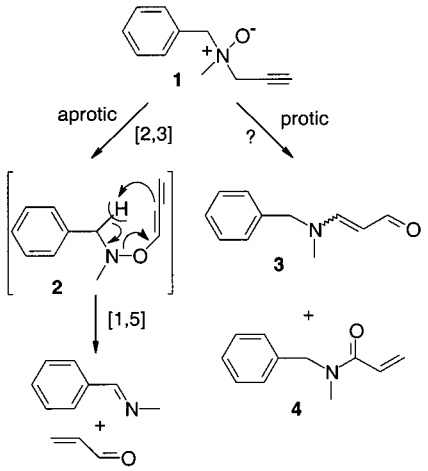
In medicinal chemistry, propargylamines are considered to be suicide inhibitors,[1] and their outstanding representatives (e.g., pargyline[2] and selegiline[3]) have been introduced into human therapy, or used as pharmacological tools, as selective monoamine oxidase inhibitors (e.g., clorgiline[4]) or to produce experimental parkinsonism (tremorine[5]). When we studied the chemical behavior of pargyline *N*-oxide (**1**) in protic media, we recognized novel type of a solvent-dependent rearrangement of tertiary propargylamine *N*-oxides. Pargyline *N*-oxide (**1**),[6] a metabolite[7] of the monoamine oxidase inhibitor pargyline,[8] and similar tertiary propargylamine *N*-oxides[9−12] are known to undergo thermal Meisenheimer-type[13] concerted [2,3] sigmatropic transformation in aprotic media (CH_2Cl_2, THF, and CCl_4), for example, to yield *O*-propadienyl hydroxylamine (**2**), which readily furnishes *N*-benzylidenemethylamine and propenal by a [1,5] hydrogen shift.

Results and Discussion

In protic media, however, two new products (**3** and **4**) were isolated, whose formation can be interpreted only by an assumption of new rearrangement (Scheme 1). Whereas **1** was stable under acidic conditions (pH 1), heating in a phosphate buffer at pH 7 at 90 °C for 2 h led to the formation of enamino aldehyde **3** (66%) and its hydrolytic product, *N*-methylbenzylamine (28%). (Enamino aldehyde **3** was also prepared from *N*-methylbenzylamine with propiolaldehyde in aqueous ethanol; its spectroscopic properties are identical to those of the product isolated from the above reaction mixture of **1**.)

Scheme 1. Rearrangement Products of Pargylin *N*-Oxide (1) in Aprotic and Protic Medium



When the hydrochloride of **1** was heated in 5% aqueous $NaHCO_3$ solution at 70 °C for 1.5 h, besides enamino aldehyde **3** (55%), acrylamide **4** (1.1%) could be isolated from the reaction mixture. Compound **4** was identical to the product of the reaction of *N*-methylbenzylamine and acryloyl chloride. Compounds **3** and **4** were also obtained in 24% and 6% yields, respectively, when **1** was heated in boiling ethanol for 3 h.

From both aqueous and ethanolic media, 1−2% and 10−12% benzaldehyde (the hydrolytic product of *N*-benzylidenemethylamine), respectively, could be identified with *p*-nitrophenylhydrazine.

For the verification of the proposed mechanism, depicted in Scheme 3, we carried out isotope labeling and repeated the same experiment with the methyl derivatives **5** and **6**.

No ^{18}O isotope incorporation into products was observed when **1** was heated in ^{18}O-labeled water (10%), but deuterium-labeled enamino aldehyde **7** and acrylamide **8** could be isolated from deutero derivative of **1** (R = D), prepared in situ, in deuterium oxide. (The deuterium on C(2) in **7** could be easily changed for hydrogen in water.)

Two methyl derivatives (**5** and **6**[14]) of pargyline *N*-oxide were also included in the mechanistic studies. From **5**, only enamino ketone **9** (54%) was isolated, and no formation of amide derivative could be detected (Scheme 2).

The results of experiments in deuterium oxide and with **5** indicate that the formation of enamino aldehyde/ketone (**3**, **9**) does not involve propargyl group migration, which is the case in the Meisenheimer rearrangement.[10]

Because of the presence of the β hydrogens, compound **6** readily participates[14] in Cope elimination[15−17] to give hydroxylamine **10** and vinylacetylene in CH_2Cl_2 at 37 °C. From an aqueous solution of the *N*-oxide **6** (where Cope elimination is suppressed[18] by solvation of the *N*-oxide)

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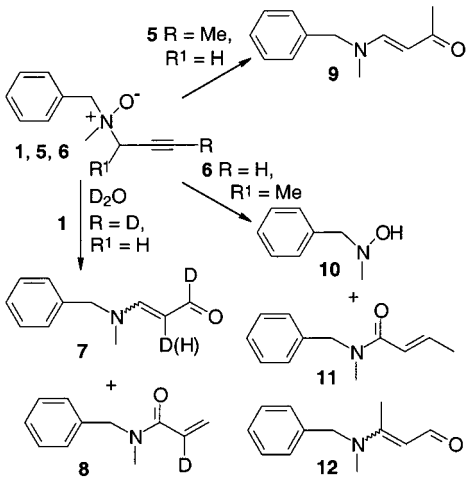
Scheme 2. Rearrangement Products of Pargylin (1) in D_2O and Its Methyl Derivatives 5 and 6 in Protic Medium



at pH 12 at 80 °C, besides hydroxylamine **10** (53%), an increased amount of crotonamide **11** (28%) was isolated. When this reaction was carried out at pH 7, the signals of enamino aldehyde **12** could be detected in the ^{1}H NMR spectrum of the crude reaction product [400.13 MHz, $CDCl_3$, δ 5.30d (=CHCO) and 9.59d (CHO, J = 8.1 Hz)].

Both the novel rearrangement and the previously known [2,3] sigmatropic rearrangement depend on the negatively charged oxide oxygen to attack the triple bond as a nucleophile (see Scheme 3). At pH 1, this oxygen is protonated so it is only very weakly nucleophilic, and therefore, *N*-oxide is stable under acidic conditions.

The above experimental data suggest that the formation of enamino aldehyde/ketone-type derivatives **16** from **13** involves a cyclic transition state **14**, similar to **14′** in the case of the Meisenheimer rearrangement[10] (path B); however, in protic medium instead of propargyl group migration by splitting of the N−C bond, the cleavage of the N−O bond (path A) occurs. After protonation, an isoxazoline **15** formed, from which by a subsequent deprotonation **16** formed. (It is interesting to note that in the case of acetylenic ammonium ylide Ollis and coworkers pointed out that beside the sigmatropic rearrangement in protic media, similar to path A, a betain cyclic structure is formed.[19,20]) The suggested mechanism, depicted in Scheme 3, is supported by the fact that the yield of enamino aldehyde **3** in water is higher than in ethanol as a consequence of the higher anion-solvating tendency of water (acity[21]) than that of ethanol.

N-Methyl-4-isoxazolinium salts (**20**), prepared by quaternization of neutral isoxazolines, were recently reported to give enamino ketones **21** and enones **22** in competing reactions, through deprotonation of the 5-CH_2 and *N*-methyl, respectively, under basic conditions[22] (Scheme 4).

During the formation of amide minor products **19**, migration of both oxygen and the propargyl group occurred. The amide minor products **19** may form via *O*-propadienyl hydroxylamine (**17**) through oxaziridinium **18**. This is supported by the formation of deuterated **8** in deuterium oxide. A similar mechanism was recently described[23] for the rearrangement of *O*-propargyl ketoximes to *N*-1-alkenylacrylamides. Rearrangement of a condensed oxaziridinium salt into a lactam has also been reported.[24]

In conclusion, the formation of enamino aldehydes and acryl amides from tertiary propargylamine *N*-oxides in protic media can be interpreted as a novel prototropic rearrangement. The proposed rearrangement mechanism is supported by isotopic labeling experiments and by relevant literature data.

Experimental Section

General Information. All reagents were of commercial quality. Phosphate buffer, pH 7.00, was purchased from Merck. Organic extracts were dried with anhydrous Na_2SO_4. Pargilin *N*-oxide (**1**),[6] *N*-(1-butin-3-yl)-*N*-methylbenzylamine *N*-oxide HCl[14] (**6**·HCl), and 1-bromo-2-butyne[25] were prepared according to the literature. Silica gel 60 (230−400 mesh, Merck) was used for column chromatography, and precoated Kieselgel 60F_{254} preparative plates (2 mm, 20 × 20, Merck) were used for preparative TLC. NMR spectra were recorded in $CDCl_3$ solution with TMS as an anternal reference at 400.13 MHz (^{1}H), and 100.61 MHz (^{13}C).

***N*-Benzyl-*N*-methyl-3-aminoacrolein (3).** To a solution of propiolaldehyde, prepared from propiolaldehyde diethyl acetal (640 mg, 5 mmol) in 0.2 N hydrochloric acid solution (5 mL) at 40 °C for 0.5 h was added dropwise a solution of *N*-methylbenzylamine (610 mg, 5 mmol) in EtOH (5 mL). After being stirred for 2 h at 50 °C, the reaction mixture was diluted with H_2O (20 mL), and EtOH was distilled off. The pH of the aqueous phase was adjusted to 12 with 1 N NaOH solution, and the reaction mixture was extracted with Et_2O. The ethereal solution was washed with H_2O. The evaporation of the dried organic phase gave an oil (830 mg) that was purified by column chromatography (benzene−acetone, 9:1) to afford enamino aldehyde **3** (500 mg, 57%). In $CDCl_3$, **3** exists as a 7:3 mixture of s-trans and s-cis rotamers:[26] IR (KBr) ν_{max} 1613 cm^{-1}; ^{1}H NMR δ 2.77 (s, 2.1H), 3.10 (s, 0.9H), 4.44 (s, 0.6H), 4.34 (s, 1.4H), 5.22 (dd, J = 8.0, 12.0 Hz, 0.7H), 5.29 (dd, J = 8.0, 12.0 Hz, 0.3H), 7.19−7.38 (m, 6H), 9.16 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 35.4, 43.0, 53.7, 61.6, 101.3, 126.9, 127.7, 128.4, 135.1, 159.9, 189.0.

***N*-Benzyl-*N*-methylacrylamide (4).** To a solution of *N*-methylbenzylamine (610 mg, 5 mmol) in acetone (10 mL) was added dropwise a solution of acryloyl chloride (490 mg, 5 mmol) in acetone (5 mL) in the presence of K_2CO_3 (690 mg) at ambient temperature. After being stirred for 1 h, the reaction mixture was filtered and the filtrate was treated with 1 N NaOH solution (20 mL). The aqueous layer was extracted with $CHCl_3$. The chloroformic solution was washed with H_2O, dried, and evaporated in vacuo to dryness. The oily residue was treated with 0.1 N hydrochloric acid for 15 min at room

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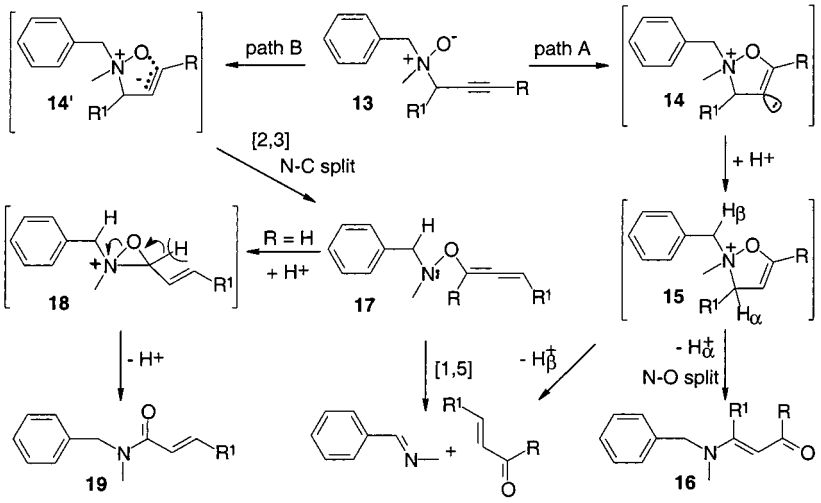
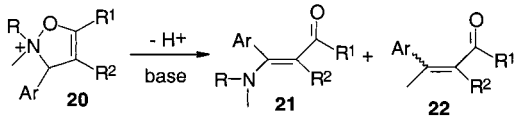
Scheme 3. Proposed Mechanism of the Rearrangement of Tertiary Propargylamine *N*-Oxides



Scheme 4



temperature, and then it was extracted with Et_2O. The dried organic solution was evaporated in vacuo to dryness to give colorless oily acrylamide **4** (610 mg, 69%). In $CDCl_3$, **4** exists as a 1:1 mixture of s-trans and s-cis amide rotamers:[26] IR (KBr) ν_{max} 1648 cm^{-1}; ^1H NMR δ 2.99 (s, 1.5H), 3.01 (s, 1.5H), 4.60 (s, 1H), 4.66 (s, 1H), 5.68 (dd, J = 10.4, 1.3 Hz, 0.5H) 5.75 (dd, J = 10.4, 1.3 Hz, 0.5H), 6.38 (dd, J = 16.7, 1.3 Hz, 0.5H), 6.41 (dd, J = 16.7, 1.3 Hz, 0.5H), 6.60 (dd, J = 10.4, 16.7 Hz, 0.5H), 6.63 (dd, J = 10.4, 16.7 Hz, 0.5H), 7.17−7.36 (m, 5H); ^{13}C NMR δ 33.8, 34.6, 50.8, 53.1, 126.1,127.0, 128.0, 127.4, 128.0, 128.2, 128.7, 136.4, 136.9, 166.3, 166.8.

Rearrangement of 1 in a Phosphate Buffer, pH 7.00. A solution of **1**·HCl (430 mg, 2 mmol) and NaOH (80 mg, 2 mmol) in a phosphate buffer, pH 7.00 (100 mL), was stirred at 90 °C for 2 h. The reaction mixture was cooled to room temperature and extracted with CH_2Cl_2. The dried organic extract was evaporated in vacuo to dryness. The residue was treated with Et_2O (15 mL). Decanted ethereal solution was evaporated to give oily enamino aldehyde **3** (230 mg, 66%). From the aqueous phase, after adjustment of pH to 13 with 10% NaOH solution, and extraction with CH_2Cl_2, then evaporation of the dried organic extract *N*-methylbenzylamine HCl (90 mg, 28%, mp 263 °C (lit.[27] mp 262−263 °C)) was obtained by the treatment of the ethereal solution of the residue with HCl gas.

Rearrangement of 1 in Ethanol. A solution of **1** (500 mg, 2.9 mmol) in EtOH (10 mL) was heated at reflux for 3 h. After evaporation of the reaction mixture, the residue was dissolved in 0.1 N hydrochloric acid (10 mL), and the aqueous phase was extracted with benzene. The dried organic phase was evaporated in vacuo to dryness. The residue was treated with Et_2O (30 mL). Decanted ethereal solution was concentrated. The preparative TLC (benzene−acetone, 3:1) of the light brown oil gave benzaldehyde, acrylamide **4** (30 mg, 6%), and enamino aldehyde **3** (20 mg, 4%). From the acidic aqueous solution, after adjustment of pH to 12 with 1 N NaOH solution, by extraction with benzene, and by evaporation of dried organic phase a second corp of enamino aldehyde **3** (100 mg, 20%) was obtained from the oily residue (170 mg) by preparative TLC.

Rearrangement of 1 in $NaHCO_3$ Solution. A solution of **1**·HCl (4.23 g, 20 mmol) and $NaHCO_3$ (2.02 g, 24 mmol) in H_2O (40 mL) was stirred at 70 °C for 1.5 h. The aqueous reaction mixture was cooled to room temperature and extracted with $CHCl_3$. The dried organic layer was evaporated in vacuo to dryness. Column chromatography (benzene−acetone, 9:1) of the oily residue (2.89 g) gave benzaldehyde (70 mg), acrylamide **4** (40 mg, 1.1%), and enamino aldehyde **3** (1.92 g, 55%).

***N*-(2-Butin-1-yl)-*N*-methylbenzylamine *N*-Oxide Hydrochloride (5·HCl).** To a solution of *N*-methylbenzylamine (3.63 g, 30 mmol) in acetone (40 mL) was added dropwise a solution of 1-bromo-2-butyne[25] (4.4 g, 33 mmol) in acetone (20 mL) in the presence of K_2CO_3 (8.28 g), and the reaction mixture was stirred at room temperature for 5 h. The excess of K_2CO_3 was filtered off. The filtrate was evaporated in vacuo to dryness. The residue was dissolved in 1 N hydrochloric acid solution (60 mL), which was extracted with ethyl acetate, then the pH of aqueous solution was adjusted to 12 with 1 N NaOH solution and extracted with $CHCl_3$. The dried organic phase was evaporated in vacuo to dryness, and the residue was treated with Et_2O (100 mL). The decanted ethereal solution was evaporated to give *N*-(2-butin-1-yl)-*N*-methylbenzylamine (2.69 g, 55%) as a colorless oil.

N-(2-Butin-1-yl)-*N*-methylbenzylamine (2.04 g, 11.8 mmol) was oxidized in $CHCl_3$ (40 mL) with *m*-CPBA (4.46 g, 13 mmol) at 5 °C for 1.5 h. To the reaction mixture was added EtOH saturated with HCl gas (15 mL), and the reaction mixture was evaporated. The residue was first treated with Et_2O (40 mL), and then it was recrystallized from a 1:1 mixture of Et_2O and acetone and finally from acetone to afford HCl salt of *N*-oxide **5** (820 mg, 31%. mp 132−133 °C): ^1H NMR δ 2.01 (s, 3H), 3.61 (s, 3H), 4.32 (d, J = 16.1 Hz, 1H), 4.48 (d, J = 16.1 Hz, 1H), 4.88 (d, J = 12.8 Hz, 1H), 5.03 (d, J = 12.8 Hz, 1H), 7.35−7.67 (m, 5H), 12.7 (brs, 1H).

Rearrangement of 5·HCl in Water in the Presence of NEt_3. A solution of **5**·HCl (450 mg, 2 mmol) and

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NEt_3 (242 mg, 2.4 mmol) in H_2O (10 mL) was stirred at 70 °C for 1.5 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 10 mL). The combined organic solution was washed with brine and H_2O, dried, and evaporated. The oily residue was dissolved in Et_2O (20 mL), the ethereal solution was filtered and evaporated. The residue was purified on preparative TLC (toluene−acetone, 3:1) to give enamino ketone **9** (200 mg, 54%) as yellow oil: ^{1}H NMR δ 2.09 (s, 3H), 2.69 (s, 3H), 4.36 (s, 2H), 5.14 (d, J = 12.0 Hz, 1H), 7.09−7.30 (m, 5H), 7.66 (d, J = 12.0 Hz, 1H).

Rearrangement of *N*-(1-Butin-3-yl)-*N*-methylbenzylamine *N*-Oxide HCl (6·HCl) in an Aqueous 0.025 N NaOH Solution. A solution of **6**·HCl[14] (330 mg, 1.46 mmol) in an aqueous 0.025 N NaOH solution (100 mL) was stirred at 80 °C for 2 h. The pH of the reaction mixture was adjusted to 1 with 1 N hydrochloric acid (40 mL), and the aqueous solution was extracted with Et_2O. The dried organic phase was evaporated, and the oily residue was purified on preparative TLC (toluene−acetone, 3:1) to afford crotonamide **11** (80 mg, 28%) as a colorless oil. In $CDCl_3$, **11** exists as a 1:1 mixture of s-trans and s-cis amide rotamers:[26] ^{1}H NMR δ 1.85 (d, J = 7.0 Hz, 1.5H), 1.91 (d, J = 7.0 Hz, 1.5H), 2.98 (s, 3H), 4.49 (s, 2H), 4.65 (s, 2H), 6.28 (d, J = 15.0 Hz, 0.5H), 6.33 (d, J = 15.0 Hz, 0.5H), 6.97 (m, 1H), 7.17−7.39 (m, 5H); ^{13}C NMR δ 18.2, 34.0, 34.8, 51.0, 53.3, 121.5, 126.2−128.8, 141.9, 166.8, 167.4.

Hydroxylamine HCl, **10**·HCl (160 mg, 53%, mp 132−133 °C, base mp 40 °C (lit.[28] mp 40−41 °C)) was obtained from the aqueous layer after the adjustment of the pH to 12 with a 1 N NaOH solution, and extraction with CH_2Cl_2, then evaporation the dried organic phase, and the saturation of the ethereal solution of the residue with HCl gas.

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