Aldol derivatives of 5-phenyl-1,4-benzodiazepin-2-on-N^4-oxide; intriguing inertness of N-oxides in aldol reactions

Dragan Šepac, Zdenko Hameršak and Vitomir Šunjić*

Ruđer Bošković Institute, Bijenička c. 54, P. O. Box 180, HR-10002 Zagreb, Croatia
E-mail: sunjic@irb.hr

Dedicated to Professor Branko Stanovnik on his 65th birthday
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Abstract
In an attempt to prepare 3-substituted 7-chloro-1,3-dihydro-1-methyl-5-phenyl-*2H*-1,4-benzodiazepin-2-on-N^4-oxides **7-10**, C(3) carbanion of 5-phenyl-1,4-benzodiazepin-2-on-N^4-oxide (**2**) proved completely inert in aldol reaction: Detour to the target compounds **7-10** via aldols **3-6** was required. Unexpected inertness of C(3) carbanion of **2** was attributed to the high charge delocalization.

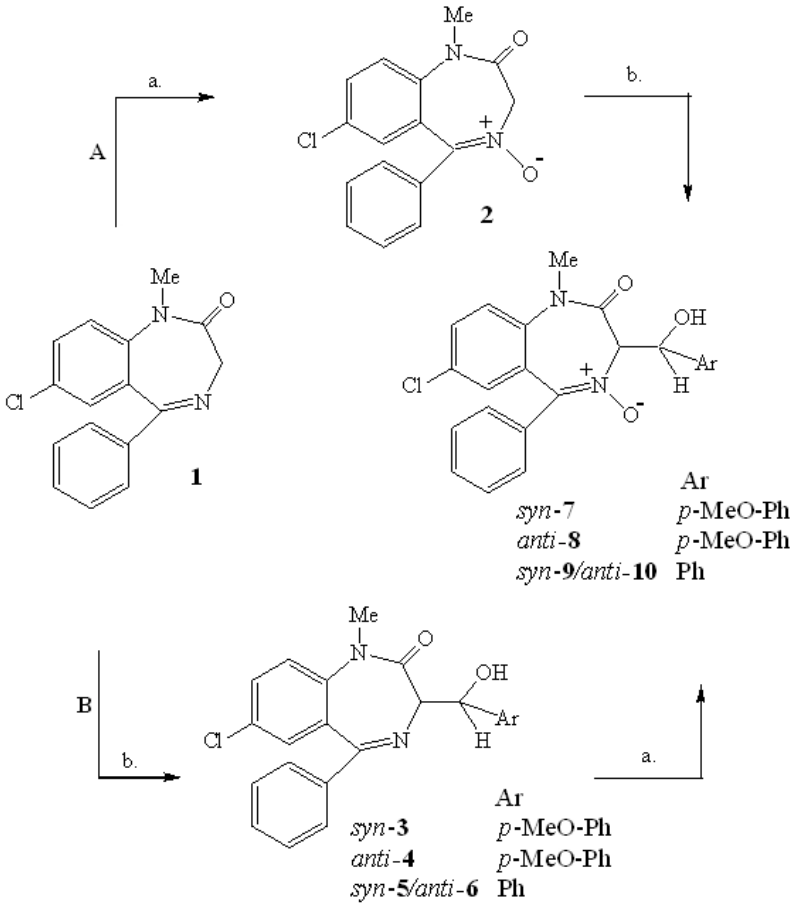
Keywords: Aldol reaction, benzodiazepines, carbanions, N-oxides

Introduction

In the course of the study of stereoselective aldol reaction of 5-phenyl-1,4-benzodiazepin-2-one[1] and its 5-pyrido- analogue[2] with aromatic and aliphatic aldehydes, we have entered the preparation of the N^4-oxides of diastereomerically pure aldol products **7-10** as potential ligands for catalytic organometallic complexes. A number of reports appeared on successful application of *N*-oxides as ligands in catalytic C-C; C-O, C-S and C-H bond forming reactions, such as allylation of aldehydes,[3,4] aldol reactions of ketones,[5] cyclopropanation of styrene,[6] epoxidations,[7] oxidation of alkenes to diols,[8] desymmetrization of epoxides,[9] addition of thiols to enones,[10.11] rearrangement of thiones to thiols.[12] Chiral β–hydroxy-*N*-oxides catalyse the enatioselective borane reduction of ketones.[13]

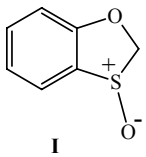
Results and Discussion

Two synthetic alternatives to the target compounds **7-10** were considered, depending whether the N-oxidation is performed before or after aldol reaction, Scheme 1, paths **A** and **B**.

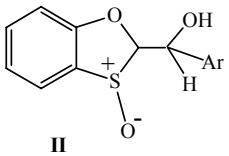


Scheme 1. a. MCPB/CH_2Cl_2/R.T, b. LDA/THF/-78°C; ArCHO.

We have selected the first approach in view of *a*. well known, technical-scale *N*-oxidation of *N*-demethyl analogue of 1,4-benzodiazepine **1** in the production of therapeutically important 3-hydroxy derivative[14] (Praxiten®, generic name Oxazepam), *b.* the observation that in the ^{1}H-NMR spectra of **1** and **2** AB system of C(3)H_2 protons is centered at 4.31 ppm and 4.64 ppm, respectively, and in their ^{13}C-NMR spectra C(3) carbon appears at 56.59 ppm and at 67.68, respectively. This reveals strong electron-deshielding effect of the N-O group and consequently higher C(3)-H acidity in **2**. The carbanion of N^4-oxide **2** is expected more convenient for the aldol reaction then carbanion of benzodiazepine **1**, similarly as the *S*-oxide function in **I** is reported by Cadoni et al.[15] to promote generation of vicinal carbanion that affords in high yield the aldol products **II**.

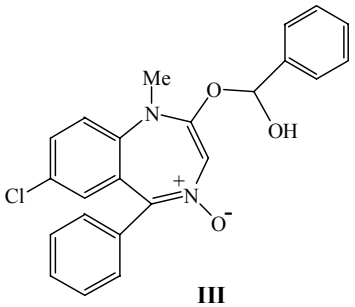


I

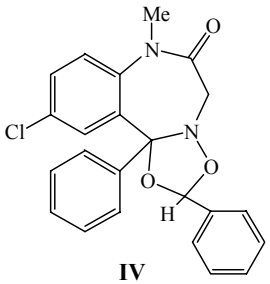


II

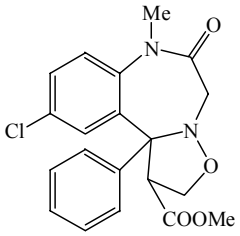
To our surprise, all attempts to complete an aldol reaction with the carbanion of **2** failed. Formation of carbanion on addition of a strong base to the THF solution of **2** can be followed by the appearance of an intense orange-red color. On addition of aldehyde this color persists and no formation of aldol product can be traced by HPLC. To the contrary, coloration disappears in few minutes at -70 °C when aldehydes are added to the solution of carbanion of **1**.[1,2] At the temperatures around 40 °C decomposition of **2** is observed. To achieve our synthetic target, the pathway **B** in the Scheme 1 was then followed; preparation of diastereomerically pure *syn* and *anti* **7** and **8** was completed by *N*-oxidation of **3** and **4**, without any loss of stereochemical integrity, as controlled by HPLC and ^{1}H-NMR. In order to test separability of the aldol products of N^4-oxides by crystallization, their deoxo-analogs can be separated only by chromatography,[1,2] diastereomeric N^4-oxides **9/10** were prepared from 4.0:6.0 mixture of **5/6**. Diastereomeric ratio remained in the product mixture but separation by crystallization failed; the products can be completely separated by chromatography. In order to explain the failed aldol reaction *of* N^4-oxide **2**, and to trace eventual side-products, additional experiments were performed. First, stability of the aldol products was checked by attempting a retro-aldol reaction of diastereomeric mixture **9/10**. HPLC monitoring has revealed their complete stability at -70 °C; on gradual elevation of temperature only *syn* diastereomer **9** has returned to **2**. In the separate experiments with *syn*-**7** and *anti*-**8**, slow splitting of **7** to **2** and benzaldehyde at temperatures between ambient and 50 °C ca be traced, whereas **8** proved stable under the same conditions.



III



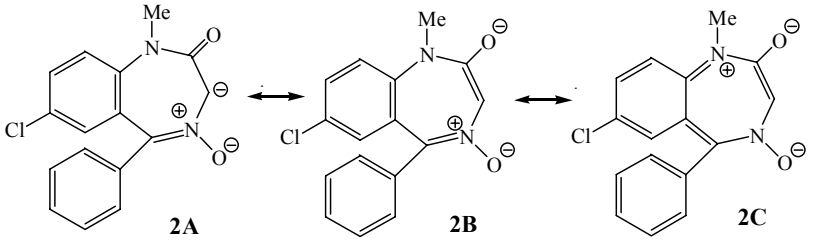
IV



V

This experiment eliminated retro-aldol reaction of the aldol products of **2** as the origin of the synthetic failure. Large difference in the stability of *syn* and *anti* diastereomers under basic conditions can be explained by different 6-membered chelate rings they form with a lithium cation. In the *syn* diastereomers chelation involves carbonyl oxygen and places the large aryl group in *pseudoequatorial* position,[1,2] whereas in the *anti*-diastereomers aryl group adopts *pseudoequatorial* conformation on chelation to the *N*-oxide oxygen atom. The former enolates only can undergo retro-aldol reaction, which is inhibited for the latter ones, however.

Aldol reaction of **2** was then monitored by HPLC under conditions that allow identification of benzoin, as the product of dimerization of benzaldehyde catalyzed by the carbanion of **2**, and eventual other side-products. No traces of benzoine have been identified, what excluded catalytic activity of the betaine-like carbanion of **2**.[16] Assuming high delocalization of the negative charge to the carbonyl and the N^4-oxide oxygen atoms, we envisaged formation of hemiacetale-like product **III** or acetal-like polycyclic product **IV**; its carbon analog **V** was reported as the addition product of *N*-oxide **2** to acrylates.[17] No such side products were identified in the reaction solution. Besides, an attempt to trap the carbanion of **2** by benzylbromide has also failed.



To explain difference in the reactivity of the carbanions of the compounds **1** and **2** we have assumed strong charge delocalization of the, lowering the electron density on the C(3) carbon. Charge-separated canonic structures have been invoked as the origin of lower inversion barrier for the 7-membered ring in N^4-oxide **2**.[18] Charge separation in the canonic structures **2A-2C** of carbanion favors delocalization of the negative charge to the oxygen atom (**2B**, **2C**); "soft" electronic nature of delocalized carbanion makes it inert in the attempted aldol reaction.

Experimental Section

General Procedures. IR spectra were run on *Perkin Elmer 297* spectrometer for KBr pallets. ^{1}H- and ^{13}C-NMR spectra were obtained with *Varian Gemini XL 300* spectrometer in $CDCl_3$, δ in ppm is relative to TMS as internal reference, and *J* in Hz. HPLC chromatography was performed on *HP 1050* chromatograph with *Nucleosil C18 RP* column, separation was monitored by *HP 1050 UV* detector set up at 254 nm and connected to *HP 3396A* integrator. M.p.'s were determined on *Electrothermal Apparatus*, and are not corrected.

Synthetic protocol for N-oxidation of 3-6. Diastereomers **3** or **4**, or diastereomeric mixture **5/6** (4.0:6.0; 1.0 g, 2.6 mmol, prepared according to ref. 1) was dissolved in CH_2Cl_2 (20 mL, filtered over the column with Alox), cooled to 0 ^oC, and over 10 min was added *meta*-chloroperbenzoic acid (MCPB; 2.1 g, 12 mmol). The reaction mixture was stirred under argon for 20 h at ambient temperature, then reaction solution was extracted with sat. aqueous $NaHCO_3$ solution (2x10mL), aqueous phase washed with EtAc (2x10 mL), organic extracts collected, dried (Na_2SO_4) and evaporated. HPLC control revealed 4.0:6.0 mixture of diasteremeric products **9/10**, which are separted by flash chromatography (50 g silicagel; *tert*-buthyl-methylether/*n*-hexane 5:2). It was obtained 0.47 g of the faster running diastereomer *anti*-**10**, and 0.53 g of the slower running *syn*-**9**.

***syn*-3-(4-Methoxyphenyl)-hydroxymethyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-*2H*-1,4-benzodiazepin-*N*^{4}-oxide (7).** The pure *syn*-**7** was obtained from *syn*-**3** in 87%, mp 205-206 ^oC (from MeOH). IR (KBr): 3435, 1684, 1611, 1514, 1484, 1443, 1406, 1251, 1181, 1114, 1033, 833 cm^{-1}. ^1H NMR ($CDCl_3$): 7.71-7.43 (m, 8H), 7.26 (s, 1H), 7.16 (d; *J*=2.3 Hz; 1H), 6.85 (d; *J*=8.6 Hz; 2H), 5.90 (d; *J*=9.4 Hz; C(3)H), 4.30 (d; *J*=9.4 Hz; C<u>H</u>OH), 3.77 (s, OMe), 3.37 (s, NMe). ^{13}C NMR ($CDCl_3$): 162.8, 159.4, 143.8, 140.0, 131.7, 131.0, 130.8, 130.6, 130.5, 130.4, 130.0, 129.4, 129.2, 129.1, 128.4, 128.1, 123.3, 113.6, 74.0, 69.8, 55.0, 35.3. Anal. calcd for $C_{24}H_{21}ClN_2O_4$ (436.89): C 65.98, H 4.84, N 6.41. Found: C 65.97, H 4.83, N 6.35%.

***anti*-3-(4-Methoxyphenyl)-hydroxymethyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-*2H*-1,4-benzodiazepin-*N*^{4}-oxide (8).** The pure *anti*-**8** was obtained from *anti*-**4** in 78% yield, mp 225-226 °C (from MeOH). IR (KBr): 3469, 1687, 1515, 1486, 1446, 1408, 1230, 1180, 1020, 840, 824, 765 cm^{-1}. ^1H NMR ($CDCl_3$): 7.54-7.39 (m, 9 H), 7.09 (d; *J*=2.2 Hz; 1H), 6.92 (d; *J*=8.5 Hz; 2H); 6.00 (d; *J*=8.5 Hz; C(3)<u>H</u>); 4.36 (d; *J*=8.5 Hz; C<u>H</u>OH); 3.83 (s, OMe), 3.57 (s, NMe). ^{13}C NMR ($CDCl_3$): 163.3, 158.6, 140.8, 134.3, 130.6, 130.5, 130.4, 130.3, 129.7, 129.3, 129.0, 128.9, 128.2, 128.1, 128.0, 124.9, 113.3, 72.4, 68.1, 55.1, 35.2. Anal. calcd for $C_{24}H_{21}ClN_2O_4$ (436.89): C 65.98, H 4.84, N 6.41. Found.: C 65.84, H 4.88, N 6.23%.

syn-3-(Phenyl)hydroxymethyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-*N*^{4}-oxide (9). After chromatographic separation and on crystallization from MeOH mp 201-202 ^oC. IR (KBr): 3552, 3447, 1664, 1482, 1410, 1296, 1215, 1109, 1036, 767, 723, 696, cm^{-1}. ^1H NMR ($CDCl_3$): 7.58-7.35 (m, 12H), 7.06 (d; *J*=1.9 Hz; 1H); 6.00 (d; *J*=8.8 Hz; C(3)H; 4.48 (d; *J*=8.8 Hz; C<u>H</u>OH), 3.51 (s, Me). ^{13}C NMR ($CDCl_3$): 165.0, 142.2, 139.9, 139.4, 131.6, 130.6, 130.4, 130.2, 130.0, 129.9, 129.8, 128.7, 128.4, 128.0, 127.8, 127.6, 127.3, 123.2, 72.8, 69.5, 35.4. Anal. Calcd for $C_{23}H_{19}ClN_2O_3$ (406.86): C. 67.90, H, 4.71, N, 6.89. Found: C, 67.54, H 4.60, N 6.83%.

***anti*-3-(Phenyl)hydroxymethyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-*2H*-1,4-benzodiazepin-*N*^{4}-oxide (10).** After chromatographic separation and on crystallization from MeOH, mp 255-256 ^oC. IR (KBr): 3441, 1686, 1486, 1443, 1407, 1207, 1044, 827, 726, 702 cm^{-1}. ^1H NMR ($CDCl_3$): 7.73-7.17 (m, 13H); 5.97 (d; *J*=9.6 Hz; C(3)H); 4.48 (s, OH), 4.35 (d; *J*=9.6 Hz; C<u>H</u>OH); 3.38 (s, Me). ^{13}C NMR ($CDCl_3$): 162.7; 144.0; 140.0; 138.0, 131.7; 131.1, 130.9, 130.8, 130.7, 130.5,

130.4, 128.4, 128.3, 128.2, 126.4, 123.3, 74.0, 70.3, 35.3. Anal. calcd. for $C_{23}H_{19}ClN_2O_3$ (406.86): C, 67.90, H, 4.71, N, 6.89. Found: C, 67.51, H, 4.41, N, 6.39%.

Acknowledgements

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