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*

Rudjer 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
(received 07 Feb 03; accepted 20 Mar 03; published on the website 15 Apr 03)

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 and its 5-pyrido-analogue 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, aldol reactions of ketones, cyclopropanation of styrene, epoxidations, oxidation of alkenes to diols, desymmetrization of epoxides, addition of thiols to enones, rearrangement of thiones to thiols. Chiral β-hydroxy-N-oxides catalyse the enatioselective borane reduction of ketones.

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.
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\textsuperscript{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\textsubscript{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 1 is reported by Cadoni et al.\textsuperscript{15} to promote generation of vicinal carbanion that affords in high yield the aldol products II.

**Scheme 1.** a. MCPB/CH$_2$Cl$_2$/R.T, b. LDA/THF/-78°C; ArCHO.
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.\textsuperscript{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 \textsuperscript{1}H-NMR. In order to test separability of the aldol products of N\textsuperscript{4}-oxides by crystallization, their deoxo-analogs can be separated only by chromatography,\textsuperscript{1,2} diastereomeric N\textsuperscript{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\textsuperscript{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 can be traced, whereas 8 proved stable under the same conditions.
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,\textsuperscript{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.\textsuperscript{16} Assuming high delocalization of the negative charge to the carbonyl and the N\textsuperscript{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.\textsuperscript{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.

\[ \begin{array}{c}
\text{Me} & \text{Cl} & \text{N} \\
\text{Cl} & \text{N} & \text{Cl} \\
\text{Me} & \text{Cl} & \text{N} \\
\text{Cl} & \text{N} & \text{Cl}
\end{array} \quad \begin{array}{c}
\text{Me} & \text{Cl} & \text{N} \\
\text{N} & \text{O} & \text{N} \\
\text{Me} & \text{Cl} & \text{N} \\
\text{N} & \text{O} & \text{N}
\end{array} \quad \begin{array}{c}
\text{Me} & \text{Cl} & \text{N} \\
\text{N} & \text{O} & \text{N} \\
\text{Me} & \text{Cl} & \text{N} \\
\text{N} & \text{O} & \text{N}
\end{array} \]

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\textsuperscript{4}-oxide 2.\textsuperscript{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. \textsuperscript{1}H- and \textsuperscript{13}C-NMR spectra were obtained with Varian Gemini XL 300 spectrometer in CDCl\textsubscript{3}, \( \delta \) 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 CH₂Cl₂ (20 mL, filtered over the column with Alox), cooled to 0 °C, 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 NaHCO₃ solution (2x10mL), aqueous phase washed with EtAc (2x10 mL), organic extracts collected, dried (Na₂SO₄) and evaporated. HPLC control revealed 4.0: 6.0 mixture of diastereomeric products 9/10, which were separated by flash chromatography (50 g silica gel; tert-butyl-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-N₄-oxide (7). The pure syn-7 was obtained from syn-3 in 87%, mp 205-206 °C (from MeOH). IR (KBr): 3435, 1684, 1611, 1514, 1484, 1443, 1406, 1251, 1181, 1114, 1033, 833 cm⁻¹. ¹H NMR (CDCl₃): 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; CH₃OH), 3.77 (s, OMe), 3.37 (s, NMe). ¹³C NMR (CDCl₃): 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, 128.1, 123.3, 113.6, 74.0, 69.8, 55.0, 35.3. Anal. calcd for C₂₄H₂₁ClN₂O₄ (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-N₄-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, 1408, 1230, 1180, 1020, 840, 824, 765 cm⁻¹. ¹H NMR (CDCl₃): 7.54-7.39 (m, 9H), 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)H); 4.36 (d; J=8.5 Hz; CH₃OH), 3.83 (s, OMe), 3.57 (s, NMe). ¹³C NMR (CDCl₃): 163.3, 158.6, 140.8, 134.3, 130.6, 130.5, 130.4, 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 C₂₄H₂₁ClN₂O₄ (436.89): C 65.97, H 4.88, N 6.35%.

syn-3-(Phenyl)hydroxymethyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-N₄-oxide (9). After chromatographic separation and on crystallization from MeOH mp 201-202 °C. IR (KBr): 3552, 3447, 1664, 1482, 1410, 1296, 1215, 1109, 1036, 767, 723, 696 cm⁻¹. ¹H NMR (CDCl₃): 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; CH₃OH), 3.51 (s, Me). ¹³C NMR (CDCl₃): 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 C₂₃H₁₉ClN₂O₃ (406.86): C 67.90, H, 4.71, N, 6.89. Found: C, 67.54, H 4.86, N 6.23%.

anti-3-(Phenyl)hydroxymethyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-N₄-oxide (10). After chromatographic separation and on crystallization from MeOH, mp 255-256 °C. IR (KBr): 3441, 1686, 1486, 1443, 1407, 1207, 1044, 827, 726, 702 cm⁻¹. ¹H NMR (CDCl₃): 7.73-7.17 (m, 13H), 5.97 (d; J=9.6 Hz; C(3)H), 4.48 (s, OMe), 4.35 (d; J=9.6 Hz; CH₃OH), 3.38 (s, Me). ¹³C NMR (CDCl₃): 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_{2}O_{3} (406.86): C, 67.90, H, 4.71, N, 6.89. Found: C, 67.51, H, 4.41, N, 6.39%.

Acknowledgements

This work was supported by the Ministry of Science and Technology of Rep. Croatia; Project No. 980701.

References