Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2020, **30**, 228–230
Mendeleev Communications

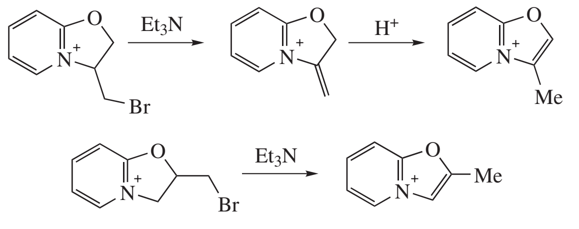
Dehydrohalogenation of isomeric 2- and 3-bromomethyl substituted 2,3-dihydrooxazolo[3,2-*a*]pyridines

Eugene V. Babaev,* Yaroslav I. Koval and Victor B. Rybakov

Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow,
Russian Federation. E-mail: babaev@org.chem.msu.ru

DOI: 10.1016/j.mencom.2020.03.033

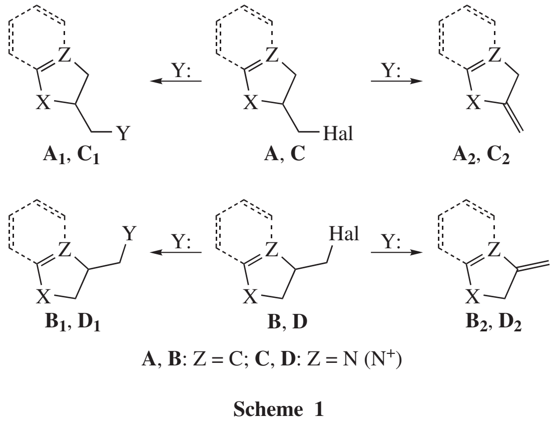
3-(Bromomethyl)dihydrooxazolo[3,2-*a*]pyridinium bromide under the action of base gives stable non-aromatic methylidene structure which can be converted into aromatic oxazolopyridinium cation only under the action of a superacid. On the contrary, 2-bromomethyl isomer under the same conditions affords only aromatic cation. The structure of the products was confirmed by X-ray diffraction.



Keywords: tautomerism, oxazoles, oxazolo[3,2-*a*]pyridinium, ring opening, X-ray diffraction.

Partially saturated 5-membered heterocycles with halomethyl groups of type **A** and **B** (Scheme 1) are important intermediates in heterocyclic chemistry. Particularly, 2,3-dihydro halomethyl derivatives of furans,[1] thiophenes,[2,3] indoles[4,5] and benzofurans[6,7] serve as important building blocks for the synthesis of biologically active and/or natural compounds. Among the reactions of halomethyl derivatives with strong nucleophiles Y^-, only in few cases (Y = CN, N_3, ArS, malonate for indoles and benzofurans[7–9]) the substitution occurred with formation of expected products $\mathbf{A_1}$ or $\mathbf{B_1}$. In most cases, however, when Y is basic enough ($Y = OH^-$ or $AlkO^-$, AcO^-, amine, Grignard reagents), formation of somewhat unusual 2(3)-*exo*-methylidene species ($\mathbf{A_2}$ and $\mathbf{B_2}$) was observed.[1,4,10] Sometimes during such dehydrohalogenations 'normal' methyl tautomers and/or their mixtures with the substitution products were formed.[3,5,11] Such strategy was found effective in design of biologically active indoles.[5]

The same is true for isomeric halomethyl derivatives of partially saturated 1,3-azoles (Z = N, X = O, S) and their *b*-fused derivatives with bridgehead nitrogen atom ($Z = N^+$, X = O, S, N, see Scheme 1). Thus, 5-(chloromethyl)-4,5-dihydrooxazoles (**C**, X = O) with amines underwent substitution of halogen to form $\mathbf{C_1}$,[12] whereas their thiazole analogs (**C**, X = S) with NaOAc formed 5-methyl derivatives *via* 5-methylidene tautomer $\mathbf{C_2}$.[13]



A, **B**: Z = C; **C**, **D**: Z = N (N^+)

Scheme 1

Bridgehead (halomethyl)dihydroimidazoles of type **D** (with fused quinoline or pyrimidine ring) under the action of basic reagents underwent transformation to *exo*-methylidene products $\mathbf{D_2}$ which were slowly converted to methyl tautomers.[14–16] (Iodomethyl)imidazo[1,2-*a*]pyrazine of type **D** in reaction with amine transformed into aromatic (methyl and aminomethyl) products.[17] Oxazoles of type **C** (fused with quinoline ring) with EtONa or R_2NH gave substitution products $\mathbf{C_1}$, whereas in reaction with alkali product $\mathbf{C_2}$ predominated.[18,19] In some cases,[20,21] opening of fused oxazole (thiazole) ring was observed.

Nothing is known on the reactions with nucleophiles/bases for the halomethyl derivatives of oxazoles with *b*-fused pyridine ring like **1a**,**b** (Scheme 2). Due to our long-years interest in the chemistry of oxazolo[3,2-*a*]pyridinium salts,[22–24] we decided to study dehydrohalogenation reactions of isomeric 2- and 3-bromomethyl derivatives of 2,3-dihydrooxazolo[3,2-*a*]pyridinium cations.

The chosen strategy involved synthesis of *N*- and *O*-allyl derivatives **2a**,**b** of 2-pyridone and their further halocyclization to 2- and 3-bromomethyl derivatives **1a**,**b** (see Scheme 2). According to ^1H NMR spectra, the signals of more aromatic pyridine ring in the molecule **2b** were shifted downfield as compared to those of **2a**, and the signal of allylic N–CH_2 was in the upper field *vs.* that of O–CH_2. Compound **2b** gave stable crystalline salt with $HClO_4$ which was characterized by X-ray diffraction (Figure 1).[†]

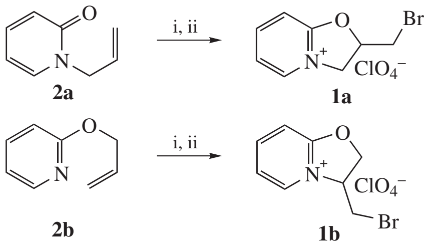
The allyl derivatives **2a**,**b** were converted into bicyclic bromomethyl derivatives of dihydrooxazolo[3,2-*a*]pyridines. To avoid

---

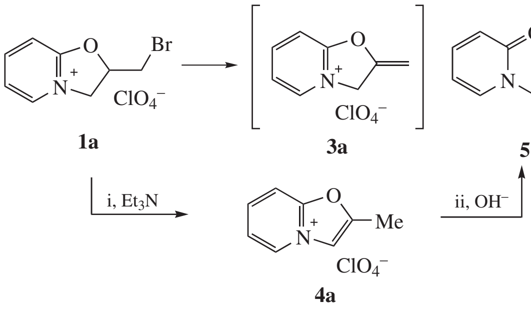
[†] *Crystal data for* **1a**. $C_8H_9BrNO^+$, ClO_4^- (*M* = 314.51), monoclinic, space group $P2_1/c$, at 295 K: *a* = 8.0912(3), *b* = 12.2638(4) and *c* = 11.2388(4) Å, β = 94.311(3)°, *V* = 1112.06(7) Å^3, *Z* = 4, d_{calc} = 1.878 g cm^{-3}, μ(CuKα) = = 7.359 mm^{-1}, R/wR_2 = 0.0503/0.1371.

Crystal data for **1b**. $C_8H_9BrNO^+$, ClO_4^- (*M* = 314.51), monoclinic, space group $P2_1/n$, at 295 K: *a* = 12.2866(6), *b* = 13.7171(7) and *c* = 14.7670(9) Å, β = 112.968(4)°, *V* = 2291.5(2 Å^3, *Z* = 8, d_{calc} = 1.823 g cm^{-3}, μ(CuKα) = = 7.142 mm^{-1}, R/wR_2 = 0.0609/0.1127.

Crystal data for **2b**. $C_8H_{10}NO^+$, ClO_4^- (*M* = 235.62), monoclinic, space group $P2_1$, at 295 K: *a* = 5.7551(4), *b* = 8.4580(8) and *c* = 10.8166(7) Å, β = 100.941(6)°, *V* = 516.95(7) Å^3, *Z* = 2, d_{calc} = 1.514 g cm^{-3}, μ(CuKα) = = 3.35 mm^{-1}, R/wR_2 = 0.0360/0.0841.



Scheme 2 *Reagents and conditions*: i, Br_2/CCl_4, room temperature, 24 h; ii, 72% $HClO_4$/EtOH.



Scheme 3 *Reagents and conditions*: i, Et_3N, room temperature, 5 h; ii, 2 equiv. K_2CO_3/H_2O, 100 °C, 3 h.

formation of tribromides, the bromomethyl derivatives were converted to perchlorates **1a**,**b** for which X-ray (Figure 2)[†] and HRMS analyses were performed. No traces of monocyclic open chain dibromides were observed according to X-ray data. The bonds in the pyridinium fragment of structure **1b** were somewhat more alternating in length than those in the structure **1a** (the latter resembled molecule **2b**). Two dihydrooxazolium bonds CO in molecule **1b** were much shorter (1.30 and 1.42 Å) than those in **1a** (1.35 and 1.47 Å). In the ^{1}H NMR spectra of **1a**,**b**, the signals of pyridinium rings were almost identical, whereas the CH_2Br signal of **1b** was in the lower field than that of **1a** and the *J* value of the former was essentially greater. In the ^{13}C NMR spectra, most downfield signals of compounds **1a**,**b** corresponded to bridgehead carbon atoms. According to HMBC, their correlation with protons H-5 and H-7 existed, and their multiplicity in ^{1}H spectra helped the assignment. The correlation between H-5 and C-3 (HMBC) allowed one to assign the C-3 in both isomers **1a** and **1b**. Ring closure of allylic ethers **2a**,**b** was somewhat similar to behavior of propargylthio derivative of pyridine.[25]

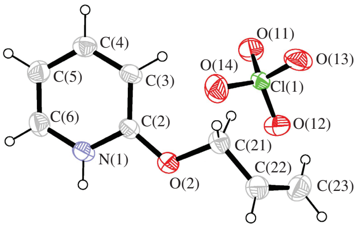


Figure 1 Molecular structure of salt **2b**·$HClO_4$.

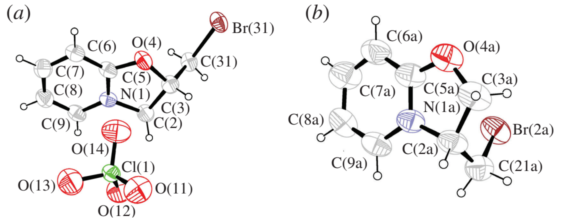
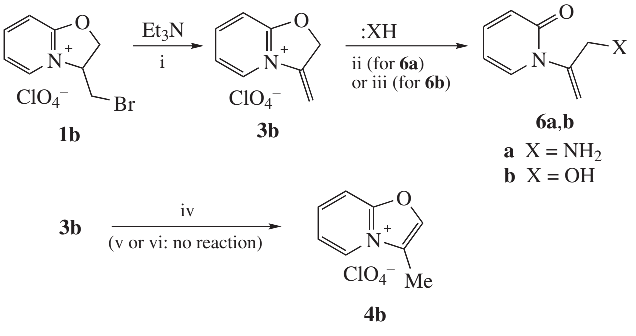


Figure 2 Molecular structures of (*a*) compound **1a** and (*b*) compound **1b** (for **1b**, anion is not shown).

Upon the action of Et_3N, isomer **1a** was converted to 2-methyloxazolo[3,2-*a*]pyridinium cation **4a** (Scheme 3). This was evident from the experiment in the NMR tube (see Online Supplementary Materials) when all the aliphatic CH_2/CH signals disappeared, and new singlets of oxazolium proton H-3 (8.53 ppm) and 2-Me-group (2.64 ppm) appeared; simultaneously, doublet H-5 was shifted downfield (9.10 ppm). In the ^{13}C NMR spectrum, the CH_2Br signal (32.9 ppm) disappeared, and instead signal Me was observed in a higher field (11.2 ppm). The aliphatic CH_2/CH signals (54.2/81.9 ppm) also disappeared, and the CH/C (113.3/119.1 ppm) signals of olefin protons emerged. This process could hardly involve the intermediate formation of 2-methylidene cation **3a**, since no new peaks (except for **1a** and **4a**) were detected during the experiment (see Online Supplementary Materials). Under the action of alkali, cation **4a** was transformed to known ring-opening product **5**.[26]

We found that, contrary to isomer **1a**, isomer **1b** upon treatment with Et_3N gave stable 3-*exo*-methylidene cation **3b** (Scheme 4), which could be separated from the mixture with Et_3NH^+ salt. Its structure, 3-methylidene-2,3-dihydooxazolo[3,2-*a*]pyridinium perchlorate, was established by X-ray study (Figure 3)[†] and HRMS data. In its ^{1}H NMR spectrum all the aliphatic CH_2/CH signals of **1b** disappeared, and new signals of oxazolium proton H-3 (5.67 ppm) and 2-CH_2-group protons (5.6 and 6.25 ppm) appeared. The *exo*-methylidene bond in the molecule of **3b** was short (1.25 Å), whereas the adjacent *endo*-bond C–CH_2 was long (1.53 Å).

Attempts to convert this cation **3b** to fully aromatic molecule **4b** (see Scheme 4) failed both with base (heating in excess of Et_3N) and with acid (CF_3COOH or 70% $HClO_4$ without heating). However, in superacidic media (CF_3SO_3H or boiling in 70% $HClO_4$), the formation of salt **4b** with fully aromatic cation was do observed. Action of nucleophiles (OH, NH_2, but not $PhNH_2$) on **3b** caused its C–O bond cleavage giving new *N*-[1-(aminomethyl)ethenyl]- or *N*-[1-(hydroxymethyl)ethenyl]pyridin-2-ones **6a**,**b**.



Scheme 4 *Reagents and conditions*: i, Et_3N, room temperature, 5 h; ii, NH_3/EtOH, room temperature; iii, K_2CO_3 (2 equiv., aq.), 100 °C, 3 h; iv, CF_3SO_3H, room temperature, 1 h; v, Et_3N, Δ, 1 day; vi, CF_3COOH, Δ, 1 day.

Crystal data for **3b**. $C_8H_8NO^+$, ClO_4^- (M = 233.6), orthorhombic, space group $P2_12_12_1$, at 295 K: a = 6.2341(4), b = 10.8378(6) and c = 14.6543(6) Å, V = 990.10(9) Å^3, Z = 4, d_{calc} = 1.567 g cm^{-3}, μ(CuKα) = 3.498 mm^{-1}, R/wR_2 = 0.0277/0.0646.

Diffraction study of compounds **1a**,**b**, **2b** and **3b** was performed on a STADIVARI Pilatus 100K single crystal diffractometer, CuKα beam with focusing mirrors. The structures were solved with the direct method using the SHELXS-97[27] program set and refined by the full-matrix least-squares technique using the SHELXL-2015[28] program set in anisotropic approximation for all non-hydrogen atoms. Hydrogen atom positions were found from difference electron density synthesis and were refined according to the ‘rider’ model. Absorption corrections were calculated with DIFABS[29] by determining equivalent reflections.

CCDC 1587645–1587647 and 1587674 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

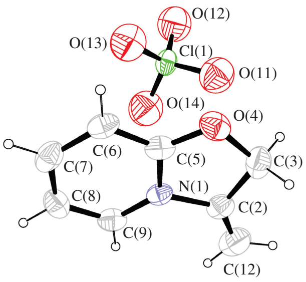


Figure 3 Molecular structure of compound **3b**.

In conclusion, dehydrobromination of two isomeric bromomethyl derivatives **1a**,**b** proceeds in two different ways, leading to formation of aromatic 2-methyloxazolopyridine **4a** and non-aromatic 3-methylidene-2,3-dihydrooxazolopyridinium derivative **3b**. Only in superacidic media compound **3b** can be converted to fully aromatic tautomer **4b**. Upon the action of alkali, compound **4a** was transformed to *N*-acetonylpyridin-2-one **5**, whereas nucleophiles opened the oxazolium ring of **3a** forming *N*-(ethenyl)-pyridin-2-one derivatives **6a**,**b**.

This work was supported by the Russian Foundation for Basic Research (grant nos. 19-53-53009 GFEN_a, 18-33-00903 Mol_a). The authors are grateful to Thermo Fisher Scientific Inc., MS Analitika (Moscow), and personally to Professor A. A. Makarov for providing the mass spectrometric equipment used in this work. The work was carried out using the equipment (STOE STADIVARI Pilatus-100K diffractometer) purchased under the Moscow State University development program.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.033.

References

1 R. N. Ram and I. Charles, *Chem. Commun.*, 1999, 2267.
2 E. Nagashima, K. Suzuki and M. Sekiya, *Tetrahedron Lett.*, 1981, **22**, 2587.
3 E. Nagashima, K. Suzuki and M. Sekiya, *Chem. Pharm. Bull.*, 1982, **30**, 4384.
4 J. H. Tidwell, D. R. Senn and S. L. Buchwald, *J. Am. Chem. Soc.*, 1991, **113**, 4685.
5 J. H Tidwell and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 11797.
6 S. Younes, Y. Labssita, G. Baziard-Mouysset, M. Payard, M.-C. Rettori, P. Renard, B. Pfeiffer and D.-H. Caignard, *Eur. J. Med. Chem.*, 2000, **35**, 107.
7 X. Yang, W. Liu, L. Li, W. Wei and C.-J. Li, *Chem. Eur. J.*, 2016, **22**, 15252.
8 R. Nagata, N. Tanno, T. Kodo, N. Ae, H. Yamaguchi, T. Nishimura, F. Antoku, T. Tatsuno, T. Kato, Y. Tanaka and M. Nakamura, *J. Med. Chem.*, 1994, **37**, 3956.
9 W. Chen, X.-D. Yang, Y. Li, L.-J. Yang, X.-Q. Wang, G.-L. Zhang and H.-B. Zhang, *Org. Biomol. Chem.*, 2011, **9**, 4250.
10 J. H. Tidwell, A. J. Peat and S. L. Buchwald, *J. Org. Chem.*, 1994, **59**, 7164.
11 V. Dichiarante, M. Fagnoni, M. Mella and A. Albini, *Chem. Eur. J.*, 2006, **12**, 3905.
12 U. Fotadar, C. Beku, F. Borremans and M. J. O. Anteunis, *Tetrahedron*, 1978, **34**, 3537.
13 U. L. Zborovskii, V. V. I. Staninets and V. V. Bon’, *Russ. J. Org. Chem.*, 2011, **47**, 881 (*Zh. Org. Khim.*, 2011, **47**, 865).
14 S. Upadhyay, A. Chandra, S. Singh and R. M. Singh, *J. Heterocycl. Chem.*, 2011, **48**, 1202.
15 A. V. Bentya, R. I. Vas’kevich, A. V. Turov, E. B. Rusanov, M. V. Vovk and V. I. Staninets, *Russ. J. Org. Chem.*, 2011, **47**, 1066 (*Zh. Org. Khim.*, 2011, **47**, 1049).
16 R. I. Vas’kevich, A. V. Bentya, A. V. Turov, E. B. Rusanov, V. I. Staninets and M. V. Vovk, *Russ. J. Org. Chem.*, 2012, **48**, 713 (*Zh. Org. Khim.*, 2012, **48**, 714).
17 P. A. Slepukhin, D. G. Kim, G. L. Rusinov, V. N. Charushin and O. N. Chupakhin, *Chem. Heterocycl. Compd.*, 2002, **38**, 1142 (*Khim. Geterotsikl. Soedin.*, 2002, **38**, 1300).
18 D. G. Kim and O. A. Schepelina, *Izv. Chelyabinskogo Nauchnogo Tsentra*, 2004, **1** (22), 149 (in Russian).
19 I. V. Ukrainets, L. V. Sidorenko, O. V. Gorokhova, S. V. Shishkina and A. V. Turov, *Chem. Heterocycl. Compd.*, 2007, **43**, 617 (*Khim. Geterotsikl. Soedin.*, 2007, **43**, 736).
20 D. G. Kim and E. A. Vershinina, *Chem. Heterocycl. Compd.*, 2014, **50**, 911 (*Khim. Geterotsikl. Soedin.*, 2014, **50**, 992).
21 I. V. Ukrainets, N. L. Bereznyakova, A. V. Turov and S. V. Shishkina, *Chem. Heterocycl. Compd.*, 2007, **43**, 871 (*Khim. Geterotsikl. Soedin.*, 2007, **43**, 1034).
22 E. V. Babaev, *Incorporation of Heterocycles into Combinatorial Chemistry*, Springer, 2017.
23 E. V. Babaev, V. L. Alifanov and A. V. Efimov, *Russ. Chem. Bull., Int. Ed.*, 2008, **57**, 845 (*Izv. Akad. Nauk, Ser. Khim.*, 2008, 831).
24 E. M. Okul’, V. B. Rybakov and E. V. Babaev, *Chem. Heterocycl. Compd.*, 2017, **53**, 997 (*Khim. Geterotsikl. Soedin.*, 2017, **53**, 997).
25 E. V. Kalita, D. G. Kim, O. S. Eltsov, T. S. Shtukina and I. V. Mukhametgaleeva, *Chem. Heterocycl. Compd.*, 2019, **55**, 473 (*Khim. Geterotsikl. Soedin.*, 2019, **55**, 473).
26 Z.-G. M. Kazhkenov, A. A. Bush and E. V. Babaev, *Molecules*, 2005, **10**, 1109.
27 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Adv.*, 2008, **64**, 112.
28 G. M. Sheldrick, *Acta Crystallogr., Sect. C: Struct. Chem.*, 2015, **71**, 3.
29 N. Walker and D. Stuart, *Acta. Crystallogr., Sect. A*, 1983, **39**, 158.

Received: 25th November 2019; Com. 19/6065