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Transformation of cyclic ketimines to oxaziridines and nitrones

Natalia G. Voznesenskaia, Olga I. Shmatova and Valentine G. Nenajdenko*

Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. Fax: +7 495 932 8846; e-mail: nenajdenko@org.chem.msu.ru

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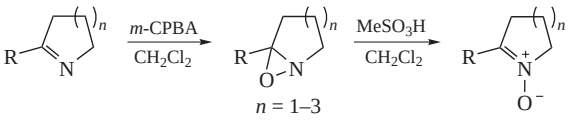
Treatment of 5-, 6- and 7-membered cyclic ketimines bearing alkyl or aryl group with *m*-chloroperbenzoic acid proceeds as C=N epoxidation and affords bicyclic oxaziridines in good yields, whose subsequent rearrangement gives nitrones.



Saturated nitrogen heterocycles are critical structural elements of wide variety of natural and bioactive compounds such as alkaloids, amino acids, drugs and potent medication candidates.[1]

Recently we have developed a convenient method for the synthesis of valuable cyclic imines with different ring size and alkyl and aryl substituents in α-position.[2] This work is devoted to investigation of oxidation of cyclic ketimines to obtain various bicyclic oxaziridines and the corresponding nitrones. Oxaziridines are very promising compounds, as outlined in reviews.[3] The literature reveals one example of natural compound containing oxaziridine fragment (Gelseziridine,[4] Figure 1). On the other hand, nitrones are widely used in organic synthesis as useful tools for constructing structurally complex molecules, usually allowing a high degree of diastereocontrol in [2+3]-cycloaddition.[5] Nitrones are employed as radical traps as well as probes for some biological systems.[6] Five- or six-membered cyclic nitrones represent crucial structural unit of many natural alkaloids, for example, Huperzine J and K obtained from *Huperzia serrata*,[7] Notoamide U,[8] Alschomine,[9] Plakinamine isolated from *Genus Corticium*[10] (see Figure 1).

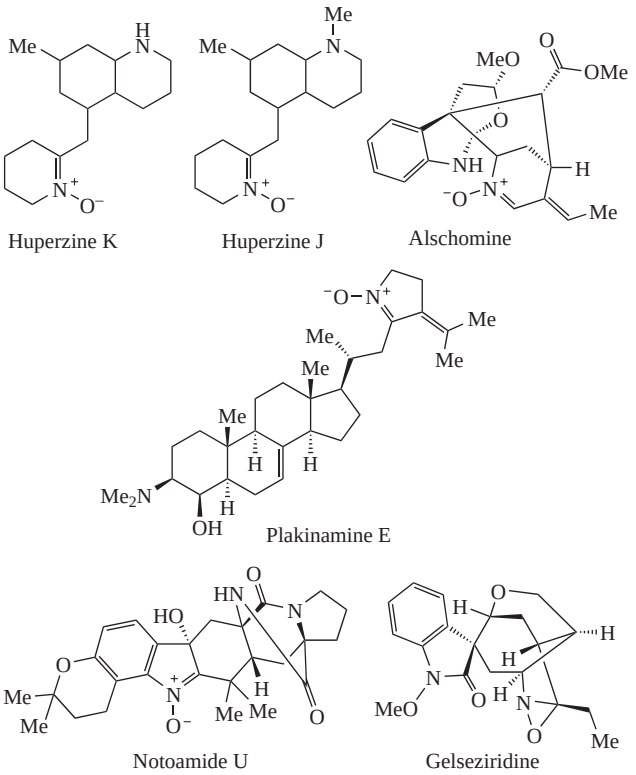


Figure 1 Some examples of natural oxaziridines and nitrones.

The standard method of the oxaziridine preparation includes oxidation of imines with peroxy acids, *e.g.* with *m*-chloroperbenzoic acid (*m*-CPBA).[11] Keeping in mind the importance of oxaziridines and cyclic nitrones, we investigated oxidation of cyclic ketimines **1a**–**k**. The set of substrates having different ring size (5–7-membered) and substituents in α-position (alkyl and aryl) was examined to have insight into the scope of such approach and influence of nature of cyclic ketimines on the reaction. Notably, this approach works perfectly well for all imines studied without significant influence of ring size and substituents on the reaction. The oxidation proceeds smoothly overnight at room temperature giving the target bicyclic oxaziridines **2a**–**k** in high yields (Scheme 1).† However, cooling of the reaction

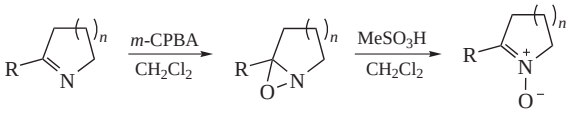
† Starting cyclic imines were synthesized according to the published procedure.[12]

General procedure for oxidation of cyclic imines **1**. The oxidant *m*-CPBA (70–75%, 1.22–1.30 mmol, 300 mg) was added to the solution of cyclic imine **1** (1 mmol) in CH_2Cl_2 (2–3 ml) at room temperature (at –15 °C in the case of **2g** and **2h**), and the mixture was stirred overnight. Then triethylamine (1.5 mmol, 0.21 ml) was added, and the crude product was purified by column chromatography (eluent CH_2Cl_2) to afford the target bicyclic oxaziridines **2**.

5-Butyl-6-oxa-1-azabicyclo[3.1.0]hexane **2a**: 62%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (t, 3H, Me, $^3J_{HH}$ 7.2 Hz), 1.27–1.42 (m, 4H), 1.54–1.63 (m, 2H), 1.70–1.81 (m, 3H), 2.18–2.24 (m, 1H), 2.81–2.88 (m, 1H), 3.36 (ddd, 1H, CH_2N, $^2J_{HH}$ 14.2 Hz, $^3J_{HH}$ 6.9 Hz, $^3J_{HH}$ 1.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 19.6, 22.6, 26.6, 28.6, 32.0, 55.2 (CH_2N), 90.3 (C_q). IR (ATR, ZnSe, ν/cm^{-1}): 2958, 1459, 1381. HRMS (ESI), *m*/*z*: 142.1229 $[M+H]^+$ (calc. for $C_8H_{16}NO^+$, *m*/*z*: 142.1227).

5-Phenyl-6-oxa-1-azabicyclo[3.1.0]hexane **2e**: 94%, colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.73–1.86 (m, 2H), 2.31–2.39 (m, 1H), 2.65–2.69 (m, 1H), 3.06–3.12 (m, 1H), 3.54 (ddd, 1H, CH_2N, $^2J_{HH}$ 14.2 Hz, $^3J_{HH}$ 7.5 Hz, $^3J_{HH}$ 1.2 Hz), 7.37–7.39 (m, 3H), 7.52–7.54 (m, 2H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.5, 27.8, 55.6 (CH_2N), 87.8 (C_q), 127.1 (Ph), 128.2 (Ph), 129.2 (Ph), 135.1 (C_q–Ar). IR (ATR, ZnSe, ν/cm^{-1}): 2964, 1451, 1355, 757, 697. HRMS (ESI), *m*/*z*: 162.0913 $[M+H]^+$ (calc. for $C_{10}H_{12}NO^+$, *m*/*z*: 162.0914).

For characteristics of compounds **2b**–**d**,**f**–**k**, see Online Supplementary Materials.



1a–k **2a–k** **3e–i,k**

n = 1–3

Imine	n	R	Oxaziridine		Nitrone	
1a	1	Bu	**2a**	(62%)		
1b	1	cyclohexyl	**2b**	(87%)		
1c	1	1-adamantyl	**2c**	(96%)		
1d	1	2-$MeC_6H_4CH_2$	**2d**	(82%)		
1e	1	Ph	**2e**	(94%)	**3e**	(99%)
1f	1	4-$MeOC_6H_4$	**2f**	(76%)	**3f**	(97%)
1g	1	4-FC_6H_4	**2g**	(93%)	**3g**	(99%)
1h	2	cyclohexyl	**2h**	(77%)	**3h**	(47%)
1i	2	Ph	**2i**	(76%)	**3i**	(99%)
1j	3	Bu	**2j**	(77%)		
1k	3	Ph	**2k**	(85%)	**3k**	(99%)

Scheme 1

mixture was necessary in the case of aryl-substituted imines **1f** and **1g** to prevent side transformations.

Then we investigated the rearrangement of prepared oxaziridines **2a–k** into the corresponding nitrones **3a–k** (see Scheme 1).‡ According to our experiments, aryl-substituted oxaziridines **2e–g** and **2k** were converted efficiently (up to 99% yields) into nitrones **3e–g** and **3k** using excess of methanesulfonic acid (3 equiv.) at room temperature. In the case of alkyl-substituted oxaziridines **2a–d** and **2j** the reaction was more complicated and no desired products were isolated. Only oxaziridine **2h** containing alkyl group and bearing six-membered ring turned into target nitrones **3h** in the presence of excess of methanesulfonic acid in 47% yield. We tried some other conditions for isomerization of imines with aliphatic substituents. However, in all cases the results were unsuccessful. For example, attempted isomerization of **2b** by neat application of CF_3COOH (6 equiv.), $MeSO_3H$ (3 equiv.)/CH_2Cl_2, TMSOTf (3 equiv.)/CH_2Cl_2 resulted in formation of complex reaction mixture and tarring. Also in reactions with $BF_3{\cdot}Et_2O$ (1 equiv.)/CH_2Cl_2, $ZnCl_2$ (1 equiv.)/CH_2Cl_2, TMSOTf (0.2 equiv.)/CH_2Cl_2, TsOH (1 equiv.)/CH_2Cl_2, CF_3COOH (1 equiv.)/CH_2Cl_2, CF_3SO_3H (1 equiv.)/CH_2Cl_2 no isomerization was observed. Therefore, additional investigations in this field will be necessary in future.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.01.008.

‡ *General procedure for rearrangement of oxaziridines into nitrones*. Methanesulfonic acid (1.54 mmol, 0.1 ml for **2e–g**,**i**,**k** and 1–2 ml for **2h**) was added to solution of oxaziridine (0.5 mmol) in CH_2Cl_2 (2–4 ml). The reaction mixture was stirred overnight, except for **2h** (several days, TLC control).

*5-Phenyl-3,4-dihydro-2*H*-pyrrole 1-oxide* **3e**: 99%, white solid, mp 100–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.13 (qt, 2H, $^3J_{HH}$ 7.7 Hz), 3.08–3.11 (m, 2H), 4.16 (t, 2H, CH_2N, $^3J_{HH}$ 8.0 Hz), 7.34–7.41 (m, 3H, H_{Ar}), 8.27–8.29 (m, 2H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.4, 30.7, 64.8 (CH_2N), 126.9 (Ph), 128.1 (Ph), 129.0 (C=N$^+$), 129.9 (Ph), 140.0 (C_q–Ar). IR (ATR, ZnSe, ν/cm^{-1}): 2951, 1569, 1435, 1223, 768, 694. HRMS (ESI), *m*/*z*: 162.0914 [M + H]$^+$ (calc. for $C_{10}H_{12}NO^+$, *m*/*z*: 162.0914).

*5-(4-Methoxyphenyl)-3,4-dihydro-2*H*-pyrrole 1-oxide* **3f**: 97%, white solid, mp 157–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10 (qt, 2H, $^3J_{HH}$ 7.8 Hz), 3.03–3.07 (m, 2H), 3.77 (s, 3H, OMe), 4.10–4.14 (m, 2H, CH_2N), 6.86–6.89 (m, 2H, H_{Ar}), 8.26–8.28 (m, 2H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.3, 30.7, 55.1, 64.3 (CH_2N), 113.4 (Ar), 122.0 (C_q–Ar), 128.9, 139.9 (C=N$^+$), 160.6 (C_q–Ar). IR (ATR, ZnSe, ν/cm^{-1}): 2957, 1602, 1509, 1250, 1026, 834. HRMS (ESI), *m*/*z*: 192.1021 [M + H]$^+$ (calc. for $C_{11}H_{12}NO_2^+$, *m*/*z*: 192.1020).

For characteristics of compounds **3g–i**,**k**, see Online Supplementary Materials.

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