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REGIOSELECTIVE OXIDATION OF ISOXAZOLIDINES TO KETONITRONES

Osamu Iwamoto,[1] Miyuki Sekine,[1] Hiroyuki Koshino,[2] and Kazuo Nagasawa[1]*

[1]Department of Biotechnology and Life Science, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan. knaga@cc.tuat.ac.jp

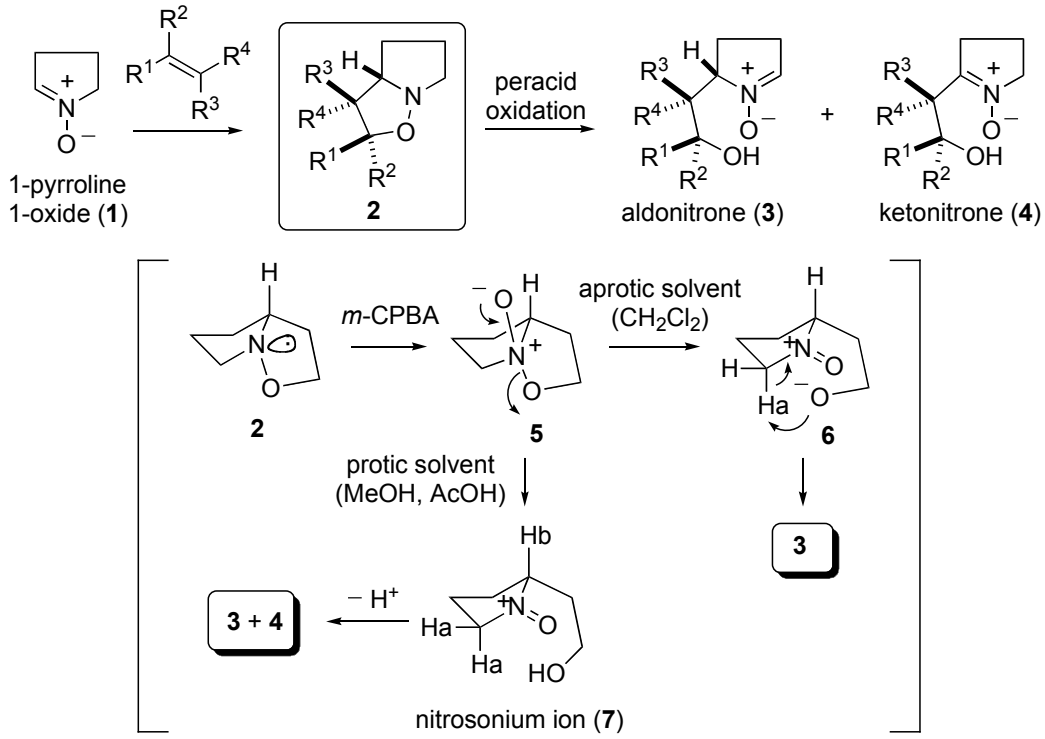
[2]RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 358-0082, Japan

Abstract – Mild and neutral conditions of *m*-CPBA-induced regioselective ring opening reaction of isoxazolidine into ketonitrone was described.

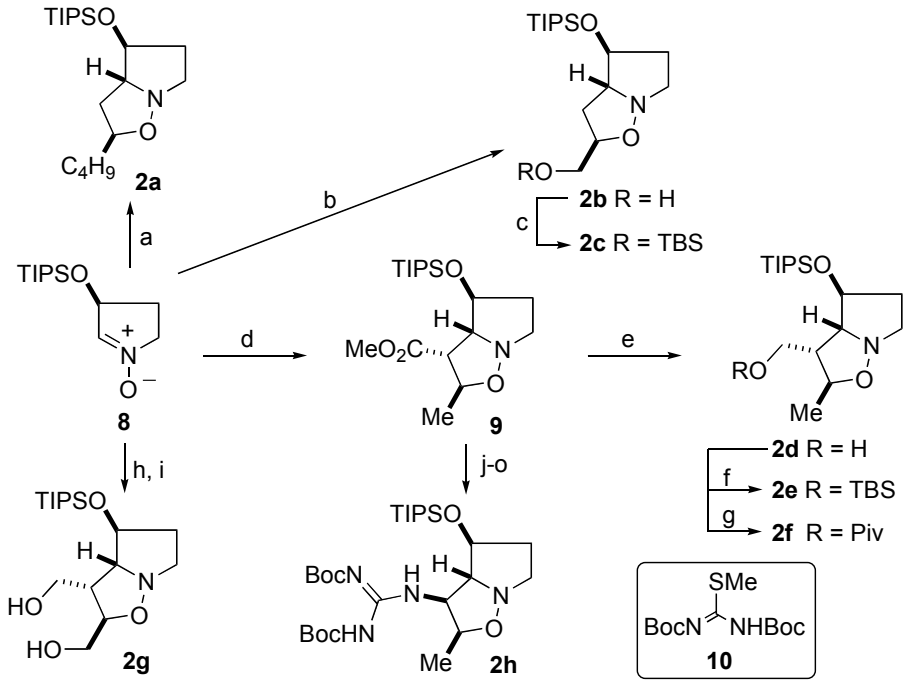
Isoxazolidines (**2**), which are obtained from 1,3-dipolar cycloaddition reaction of 1-pyrroline 1-oxide (**1**) and olefins, is regioselectively converted into aldonitrones (**3**) by peracid-induced ring opening oxidation in aprotic solvent.[1] Successive 1,3-dipolar cycloaddition reactions of aldonitrones (**3**) with olefins give useful synthetic intermediates of alkaloids having pyrrolidine and/or cyclic guanidine moieties.[2] The reaction mechanism of the peracid-induced oxidation is shown in Scheme 1.[1d,3]

In aprotic solvent, oxidation of isoxazolidines (**2**) followed by ring opening of **5** gives the nitrosonium inner salt (**6**), whose alkoxide ion abstracts the hydrogen Ha under the kinetic control to generate the aldonitrones (**3**). In contrast, the peracid oxidation of **2** in protic solvent gives a mixture of **3** and the ketonitrones (**4**) by the abstraction of Ha or Hb from the nitrosonium (**7**). In this reaction, thermodynamically stable **4** is produced as the major product; however, synthesis of "selective" ketonitrones (**4**) from **2** remains an unsolved issue despite of synthetic utility. Little effort has so far been made toward this problem, and only the case of oxidation in acetic acid with "limited substrates" was reported for the selective oxidation to ketonitrones (**4**).[3,4] Herein, we describe the mild conditions for regioselective oxidation of **2** into ketonitrones (**4**).

This paper is dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.



Scheme 1. Proposed mechanism of peracid-induced ring opening oxidation of isoxazolidine (**2**).

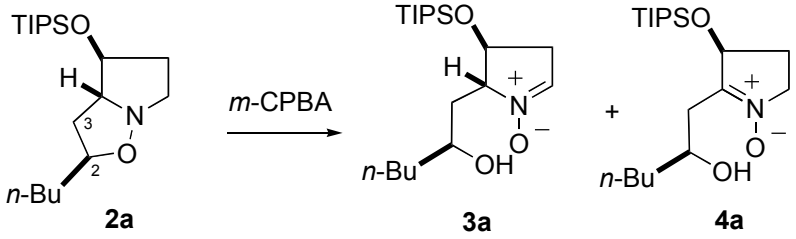


Scheme 2. Preparation of isoxazolidines (**2a**~**2h**). Reagents and conditions: (a) 1-hexene, toluene, 90 °C, 83%; (b) allyl alcohol, 100 °C, 68%; (c) TBSCl, imidazole, CH_2Cl_2, rt, 85%; (d) methyl crotonate, toluene, 80 °C, 95%; (e) $LiAlH_4$, Et_2O, 0 °C; (f) TBSCl, imidazole, DMF, rt, 99% (2 steps); (g) PivCl, pyridine, DMAP, CH_2Cl_2, rt, 97% (2 steps); (h) methyl fumalate, toluene, 80 °C, 89%; (i) $LiAlH_4$, Et_2O, 0 °C, 54%; (j) LiOH, THF/H_2O = 3:1, 0 °C, 24 h; (k) $(COCl)_2$, cat. DMF, toluene, 0 °C; (l) NaN_3/ H_2O, acetone, 0 °C; (m) toluene, 110 °C; then allyl alcohol, pyridine, 89% (4 steps); (n) $Pd(PPh_3)_4$, dimedone, THF, rt; (o) **10**, $HgCl_2$, Et_3N, DMF, rt, 58% (2 steps).

A variety of optically active isoxazolidines (**2a~2h**) were synthesized as shown in Scheme 2. Isoxazolidines (**2a**-**2c**), having alkyl, hydroxyl, and silyl ether groups at the C2 position, were prepared by 1,3-dipolar cycloaddition reaction (1,3-DC) with optically active nitrone (**8**)[5] and 1-hexene and/or allyl alcohol. Isoxazolidines having substituents at C2 and C3 positions (**2d**-**2f**, **2h**[6]) were synthesized from **9**, which was obtained by the use of 1,3-DC with **8** and methyl crotonate. Isoxazolidine diol (**2g**) was also synthesized by 1,3-DC with **8** and methyl fumarate.

Peracid oxidation was first examined using *m*-CPBA with isoxazolidine (**2a**), and the results are summarized in Table 1. Reaction of **2a** in dichloromethane selectively gave aldonitrone (**3a**), while a mixture of **3a** and **4a** was generated in methanol with a ratio of 40 : 60 (Entries 1-4). Interestingly, increasing the amounts of oxidant influenced the ratio (Entry 5), and we found that the regioselective oxidation to ketonitrone (**4a**) proceeded under the condition of 2 equiv. of *m*-CPBA at room temperature (Entry 6).[7,8] Since this reaction condition is neutral, it can be applied to acid labile substrates.

Table 1. *m*-CPBA-Induced selective ring opening reaction of isoxazolidine (**2a**).

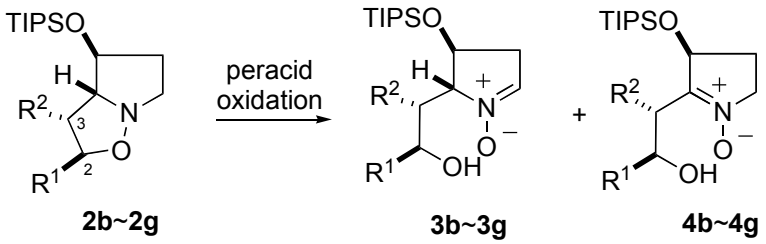


Entry	Solvents	Temp. (°C)	mCPBA (equiv.)	Time (min)	Aldonitrones[a] **3a** (% yield)	Ketonitrones[a] **4a** (% yield)	Ratio **3** / **4**
1	CH_2Cl_2	0	1.2	8	66	0	100 / 0
2	CH_2Cl_2	25	1.2	10	88	0	100 / 0
3	MeOH	0	1.2	6	40	60	40 / 60
4	MeOH	25	1.2	6	32	47	40 / 60
5	MeOH	0	2.0	7	27	54	33 / 67
6	MeOH	25	2.0	10	0	78	0 / 100

[a]Isolated yield.

Oxidation of various isoxazolidines (**2b**-**g**) having substituents at C2- and/or C2 and C3-positions was examined, and the results are summarized in Table 2. When the reaction was conducted using 2~3 equiv. of *m*-CPBA in methanol at room temperature, ketonitrones (**4**) were obtained exclusively, although the yields were moderate (Entries 4, 8, 11, 15 and 18).[9] It is noteworthy that a free hydroxyl group in isoxazolidine (**2**) did not affect the regioselectivity under these conditions (Entries 4 and 11).[3] Only in the case of **2g**, having two hydroxyl groups at C2 and C3 positions, generated a small amount of aldonitrone (**3g**) even though 3 equiv. of *m*-CPBA were used (Entry 22).

Table 2. *m*-CPBA-induced selective ring opening reaction of isoxazolidines (**2b**~**2g**).



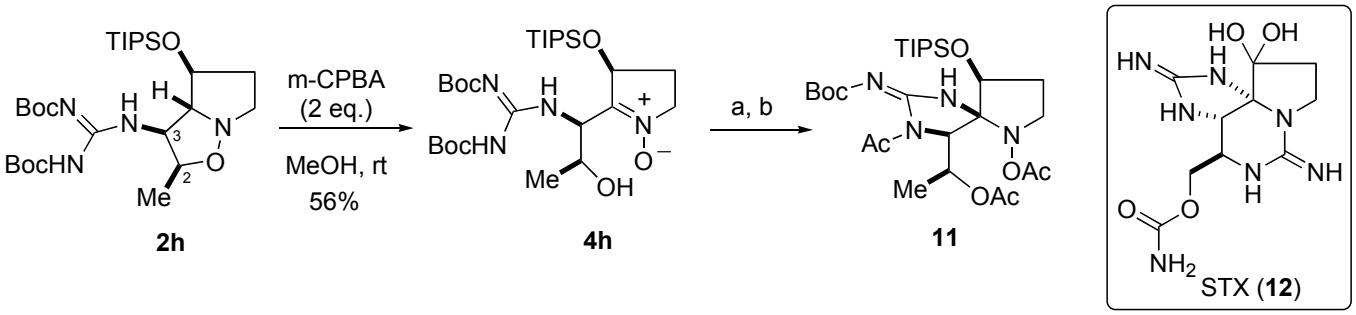
2b~2g **3b~3g** **4b~4g**

2b: $R^1 = CH_2OH$, $R^2 = H$ **2e**: $R^1 = Me$, $R^2 = CH_2OTBS$
2c: $R^1 = CH_2OTBS$, $R^2 = H$ **2f**: $R^1 = Me$, $R^2 = CH_2OPiv$
2d: $R^1 = Me$, $R^2 = CH_2OH$ **2g**: $R^1 = R^2 = CH_2OH$

Entry	Isoxazolidines	Solvents	Temp. (°C)	mCPBA (equiv.)	Time (min)	Aldonitrones **3** (% yield)	Ketonitrones **4** (% yield)	Ratio[a] **3** / **4**
1	**2b**	CH_2Cl_2	0	1.2	10	77	0	100 / 0
2	**2b**	MeOH	0	2.0	10	24	48	33 / 67
3	**2b**	MeOH	25	2.0	10	12	34	21 / 79
4	**2b**	MeOH	25	3.0	10	0	48	0 / 100
5	**2c**	CH_2Cl_2	0	1.2	10	80	0	100 / 0
6	**2c**	MeOH	0	2.0	10	27	38	41 / 59
7	**2c**	MeOH	25	2.0	10	11	49	18 / 82
8	**2c**	MeOH	25	3.0	10	0	50	0 / 100
9	**2d**	CH_2Cl_2	0	1.2	10	53	0	100 / 0
10	**2d**	MeOH	0	2.0	10	5	61	8 / 92
11	**2d**	MeOH	25	2.0	15	0	70	0 / 100
12	**2e**	CH_2Cl_2	0	1.2	12	74	0	100 / 0
13	**2e**	MeOH	0	1.2	15	13	39	25 / 75
14	**2e**	MeOH	0	2.0	10	15	42	26 / 74
15	**2e**	MeOH	25	2.0	10	0	38	0 / 100
16	**2f**	CH_2Cl_2	0	1.2	10	60	0	100 / 0
17	**2f**	MeOH	0	2.0	10	0	52	0 / 100
18	**2f**	MeOH	25	2.0	10	0	56	0 / 100
19	**2g**	CH_2Cl_2	0	1.2	20	68	0	100 / 0
20	**2g**	MeOH	0	2.0	15	33	48	40 / 60
21	**2g**	MeOH	25	2.0	10	5	45	10 / 90
22	**2g**	MeOH	25	3.0	15	5	53	8 / 92

[a]The ratios of **3** and **4** were determined by ^1H NMR.[3]

Finally, synthetic utility of ketonitrone (**4**) was demonstrated in Scheme 3. Isoxazolidine (**2h**), having guanidine group at C3 position, was reacted with *m*-CPBA (2 equiv.) in methanol at room temperature to give **4h** exclusively in 56% yield. Deprotection of one of the two Boc groups of **4h** was conducted by $TiCl_4$ (2 equiv.) at –40 °C and simultaneous cyclization took place to generate spiro-guanidine. The resulting hydroxylamine of the spiro-guanidine was treated with acetic anhydride to give **11**, which is a useful intermediate for the synthesis of saxitoxin (STX) (**12**).[10,11,12]



Scheme 3. Peracid-induced ring opening reaction of **2h**, and application to the synthesis of spiro-guanidine compound (**11**). Reagents and conditions; (a) $TiCl_4$, CH_2Cl_2, MS4A, -40 °C, 60%, (22% of **4h** was recovered), (b) Ac_2O, pyridine, rt, 52%.

In summary, we have found regioselective oxidation conditions of isoxazolidines (**2**) into ketonitrones (**4**) by using 2 equiv. of *m*-CPBA in methanol. Since ketonitrone (**4**), as well as aldonitrone (**3**), is a useful synthetic precursor for the naturally occurring alkaloids, further application studies for the synthesis of natural products using this methodology are in progress.

ACKNOWLEDGEMENTS

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3. Sk. A. Ali and M. I. M. Wazeer, *Tetrahedron*, 1993, **49**, 4339.
4. Ali et al. reported regioselective oxidation of isoxazolidines to ketonitrones in acetic acid.[3] However, in case of **2a**, mixture of **3a** and **4a** (~1 : 3) was obtained under the reaction conditions reported by Ali, i.e., 1.2 equiv. of *m*-CPBA in acetic acid at room temperature.

5. Preparation of optically active nitrone (**8**); A. Goti, M. Cacciarini, F. Cardona, A. Brandi, *Tetrahedron Lett*., 1999, **40**, 2853
6. In the reaction of **9** with lithium hydroxide at 0 °C, isomerization at C3 position took place and the subsequent hydrolysis occurred to give the corresponding carboxylic acid exclusively. When this hydrolysis reaction was performed at room temperature, a mixture of α- and β-carboxylic acids at the C3 position was obtained (ratio: ~1:1). Relative stereochemistry of **2h** was determined by nOe using the compound after the Curtius rearrangement.
7. Isomerization between aldonitrone (**3a**) and ketonitrone (**4a**) was not observed under the reaction conditions.
8. Two equiv. of *m*-CPBA is required for the regioselective oxidation to ketonitrone (**4**), however, the role of the extra one equiv. of *m*-CPBA is not clear at this stage.
9. Typical procedure for the *m*-CPBA-induced regioselective ring opening oxidation of isoxazolidine (**2c**). To a solution of isoxazolidine (**2c**) (26 mg, 0.06 mmol) in MeOH (1 mL) was added *m*-CPBA (77%, 40 mg, 0.18 mmol) at rt, and the resulting mixture was stirred for 10 min. $Na_2S_2O_3$ aqueous solution was added to the reaction mixture, and the organic layer was extracted with EtOAc. Extracts were washed with sat-$NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent; hexane : EtOAc = 3 : 1) to give **4c** (13 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (brs, 1H), 4.11 (m, 1H), 3.96 (m, 2H), 3.67 (dd, J = 5.0, 10.0 Hz, 1H), 3.54 (dd, J = 6.9, 10.0 Hz, 1H), 2.76 (m, 3H), 2.56 (m, 1H), 1.08 (m, 21H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).
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12. Spectral data for **11**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.23 (s, 1H), 5.28 (dq, J = 3.5, 6.6 Hz, 1H), 4.3 (d, J = 3.5 Hz, 1H), 4.15 (brdd, J = 5.0, 4.0 Hz, 1H), 3.25 (m, 1H), 3.01 (m, 1H), 2.64 (s, 3H), 2.10 (m, 1H), 2.04 (s, 3H), 2.00 (m, 1H), 1.93 (s, 3H), 1.48 (s, 9H), 1.30 (d, J = 6.6 Hz, 3H), 1.01 (brs, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.41, 169.70, 167.96, 162.94, 158.60, 86.13, 79.54, 75.92, 67.97, 62.57, 53.66, 30.46, 27.98, 25.32, 21.09, 19.22, 18.12, 17.82, 12.32.