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REGIOSELECTIVE OXIDATION OF ISOXAZOLIDINES TO KETONITRONES

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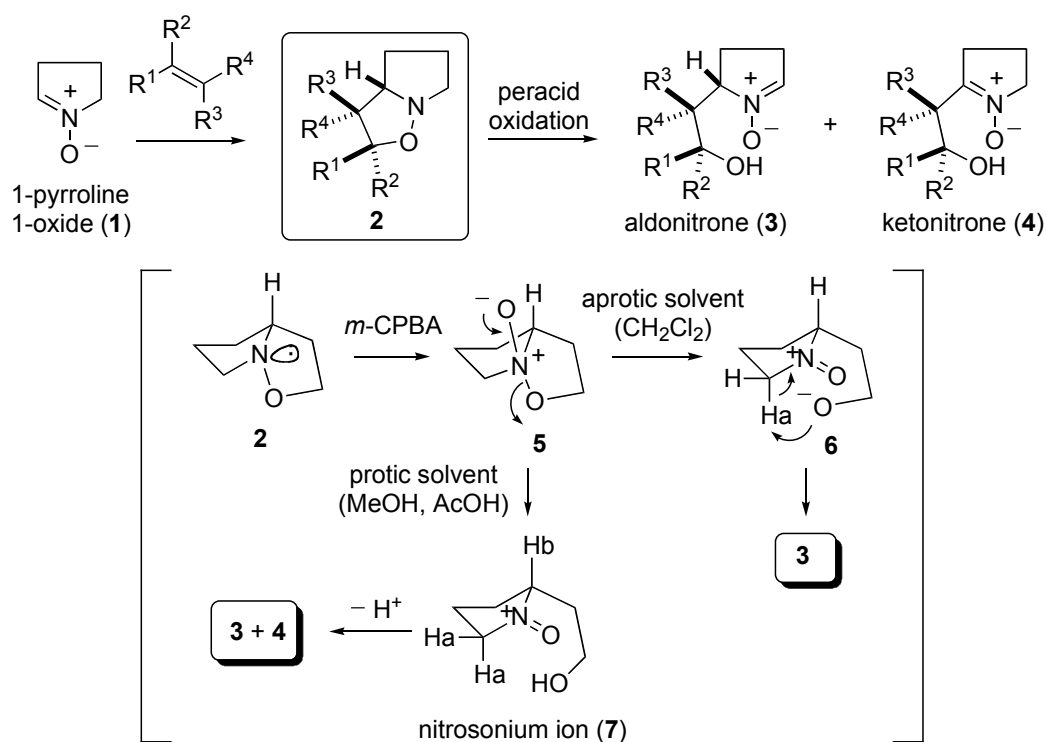
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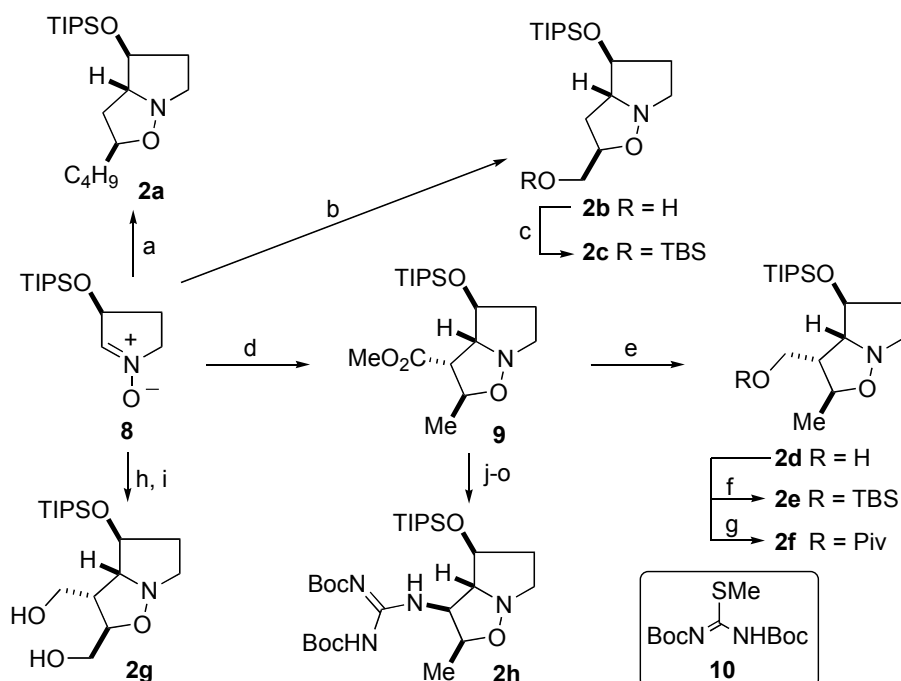
Abstract – Mild and neutral conditions of *m*-CPBA-induced regioselective ring opening reaction of isoxazolidine into ketonitrone was described.

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**).



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

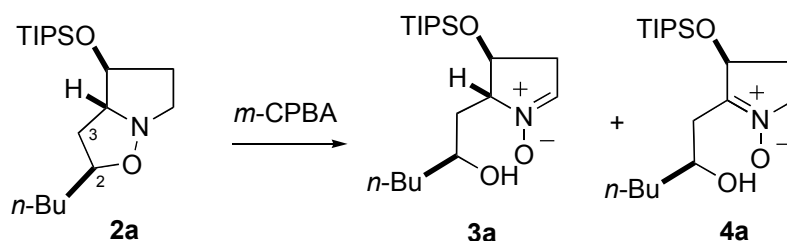


Scheme 2. Preparation of isoxazolidines (2a~2h). Reagents and conditions: (a) 1-hexene, toluene, 90 °C, 83%; (b) allyl alcohol, 100 °C, 68%; (c) TBSCl, imidazole, CH₂Cl₂, rt, 85%; (d) methyl crotonate, toluene, 80 °C, 95%; (e) LiAlH₄, Et₂O, 0 °C; (f) TBSCl, imidazole, DMF, rt, 99% (2 steps); (g) PivCl, pyridine, DMAP, CH₂Cl₂, rt, 97% (2 steps); (h) methyl fumalate, toluene, 80 °C, 89%; (i) LiAlH₄, Et₂O, 0 °C, 54%; (j) LiOH, THF/H₂O = 3:1, 0 °C, 24 h; (k) (COCl)₂, cat. DMF, toluene, 0 °C; (l) NaN₃/H₂O, acetone, 0 °C; (m) toluene, 110 °C; then allyl alcohol, pyridine, 89% (4 steps); (n) Pd(PPh₃)₄, dimedone, THF, rt; (o) 10, HgCl₂, Et₃N, 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 nitrene (**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.

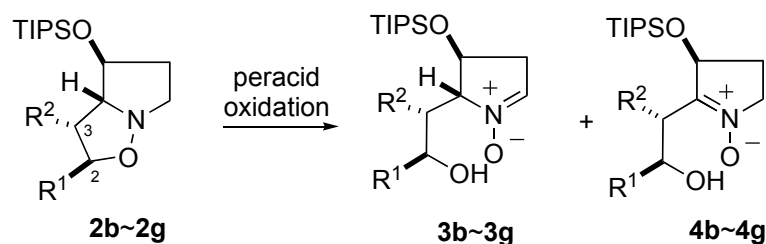
Table 1. *m*-CPBA-Induced selective ring opening reaction of isoxazolidine (**2a**).



Entry	Solvents	Temp. (°C)	<i>m</i> CPBA (equiv.)	Time (min)	Aldonitrones ^a 3a (% yield)	Ketonitrones ^a 4a (% yield)	Ratio 3 / 4
1	CH ₂ Cl ₂	0	1.2	8	66	0	100 / 0
2	CH ₂ Cl 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

^aIsolated yield.

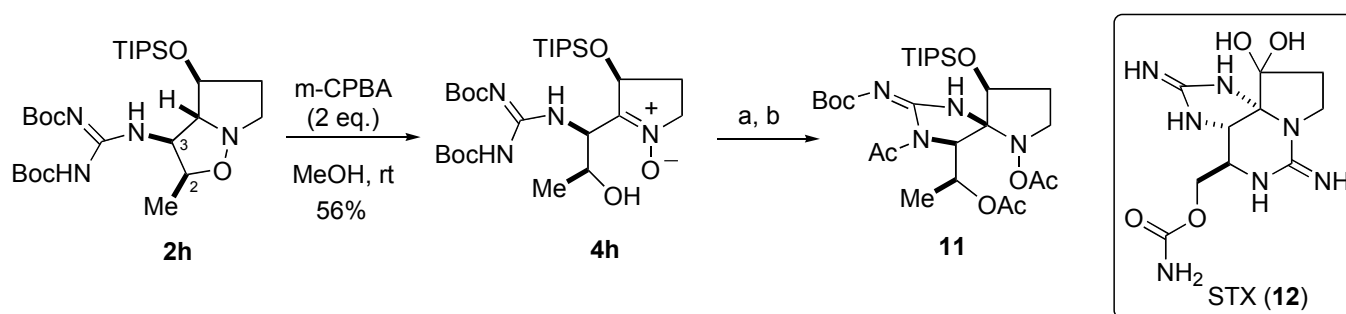
Oxidation of various isoxazolidines (**2b-g**) having substituents at C2- and/or C2 and C3-positions was examined, and the results are summarized in Table 2. When the reaction was conducted using 2~3 equiv. of *m*-CPBA in methanol at room temperature, ketonitrones (**4**) were obtained exclusively, although 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**: R¹ = CH₂OH, R² = H**2e**: R¹ = Me, R² = CH₂OTBS**2c**: R¹ = CH₂OTBS, R² = H**2f**: R¹ = Me, R² = CH₂OPiv**2d**: R¹ = Me, R² = CH₂OH**2g**: R¹ = R² = CH₂OH

Entry	Isoxazolidines	Solvents	Temp. (°C)	<i>m</i> CPBA (equiv.)	Time (min)	Aldonitrones	Ketonitrones	Ratio ^a 3 / 4
						3 (% yield)	4 (% yield)	
1	2b	CH ₂ Cl 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 ₂ Cl 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 ₂ Cl 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 ₂ Cl 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 ₂ Cl 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 ₂ Cl 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

^aThe 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 TiCl₄ (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) TiCl₄, CH₂Cl₂, MS4A, -40 °C, 60%, (22% of **4h** was recovered), (b) Ac₂O, pyridine, rt, 52%.

In summary, we have found regioselective oxidation conditions of isoxazolidines (**2**) into ketonitrone (**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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REFERENCES AND NOTES

1. a) J. J. Tufariello, *Acc. Chem. Res.*, 1979, **12**, 396. b) J. J. Tufariello and Sk. A. Ali, *Tetrahedron Lett.*, 1978, **19**, 4647. c) J. J. Tufariello, J. B. Mullen, E. J. Tribulski, S. C. Wong, and Sk. A. Ali, *J. Am. Chem. Soc.*, 1979, **101**, 2435. d) Sk. A. Ali and M. I. M. Wazeer, *Tetrahedron Lett.*, 1992, **33**, 3219. e) Sk. A. Ali, and M. I. M. Wazeer, *Tetrahedron Lett.*, 1993, **34**, 137.
2. a) W. Carruthers, P. Coggins, and J. B. Weston, *J. Chem. Soc., Perkin Trans. 1*, 1991, 611. b) K. Nagasawa, A. Georgieva, H. Koshino, T. Nakata, T. Kita, and Y. Hashimoto, *Org. Lett.*, 2002, **4**, 177. c) T. Ishiwata, T. Hino, H. Koshino, T. Nakata, and K. Nagasawa, *Org. Lett.*, 2002, **4**, 2921. d) J. Shimokawa, K. Shirai, A. Tanatani, Y. Hashimoto, and K. Nagasawa, *Angew. Chem. Int. Ed.*, 2004, **43**, 1559. e) J. Shimokawa, T. Ishiwata, K. Shirai, H. Koshino, A. Tanatani, T. Nakata, Y. Hashimoto, and K. Nagasawa, *Chem. Eur. J.*, 2005, **11**, 6878.
3. Sk. A. Ali and M. I. M. Wazeer, *Tetrahedron*, 1993, **49**, 4339.
4. Ali et al. reported regioselective oxidation of isoxazolidines to ketonitrone 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 nitron (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 aldonitron (3a) and ketonitron (4a) was not observed under the reaction conditions.
8. Two equiv. of *m*-CPBA is required for the regioselective oxidation to ketonitron (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. Na₂S₂O₃ aqueous solution was added to the reaction mixture, and the organic layer was extracted with EtOAc. Extracts were washed with sat-NaHCO₃ and brine, dried over MgSO₄, 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%). ¹H NMR (400 MHz, CDCl₃) 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).
10. L. E. Llewellyn, *Nat. Prod. Rep.*, 2006, **23**, 200.
11. Total synthesis of STX (12); a) H. Tanino, T. Nakata, T. Kaneko, and Y. Kishi, *J. Am. Chem. Soc.*, 1977, **99**, 2818. b) P. A. Jacobi, M. J. Martinelli, and S. Polanc, *J. Am. Chem. Soc.*, 1984, **106**, 5594. c) J. J. Fleming and J. Du Bois, *J. Am. Chem. Soc.*, 2006, **128**, 3926.
12. Spectral data for 11: ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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.