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Oxidative Cleavage of Aryl Oxazolines Using Methyl(trifluoromethyl)dioxirane Generated *in situ*

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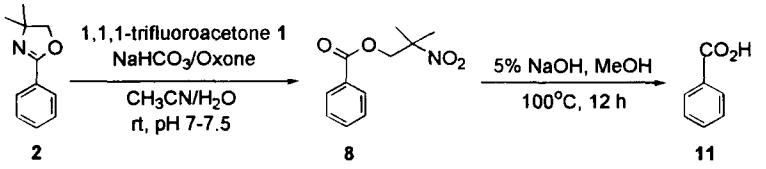
Abstract: Oxidative cleavage of aryl oxazoline **2** using methyl(trifluoromethyl)dioxirane **1a** generated *in situ* provides the intermediate nitro-ester **8**, which undergoes a basic hydrolysis to furnish benzoic acid **11**. Even the hindered oxazoline **7** can be cleaved smoothly to afford 3,3'-dimethyl-2,2'-diphenic acid **16**. All substituted benzoic acids **11**–**16** can be isolated in excellent yields (80–95 %).

Oxazolines are versatile intermediates in synthesis of aromatic compounds.[1] Both electrophilic[2a-b] and nucleophilic[2c-d] substitutions allow ready access to various *ortho*-substituted aryl oxazolines, and hydrolysis of those oxazolines provides *ortho*-substituted benzoic acids. The two most commonly used hydrolysis methods are acidic hydrolysis, and *N*-methylation followed by basic hydrolysis.[3] However, both methods require vigorous reaction conditions. Alternative methods include oxidative cleavage with sodium hypochlorite followed by a mild basic hydrolysis,[4] and reaction of oxazolines with trifluoromethanesulfonic anhydride followed by methylation and hydrolysis.[5] The former method requires relatively long reaction time (12–48 h) to cleave oxazolines under phase transfer conditions, while the latter cannot be employed for those oxazoline substrates with functional groups that react with trifluoromethanesulfonic anhydride. Here, we report a new oxidative cleavage method for aryl oxazoline hydrolysis, which is especially effective for sterically hindered oxazolines.[6]

As shown in Scheme 1, the oxidative cleavage method simply involves addition of premixed Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) and sodium bicarbonate to oxazoline **2** and 1,1,1-trifluoroacetone **1** in the CH_3CN–H_2O solvent system at room temperature.[7] The nitroester **8** was isolated as a stable intermediate, which furnished benzoic acid **11** in excellent yield upon basic hydrolysis (91% overall).

Scheme 1



As to the mechanism of oxidative cleavage, we propose that methyl(trifluoromethyl)dioxirane **1a** generated *in situ* may act as an electrophilic oxidant towards oxazoline **2** to yield the nitroester **8** (Scheme 2).[8]

Scheme 2

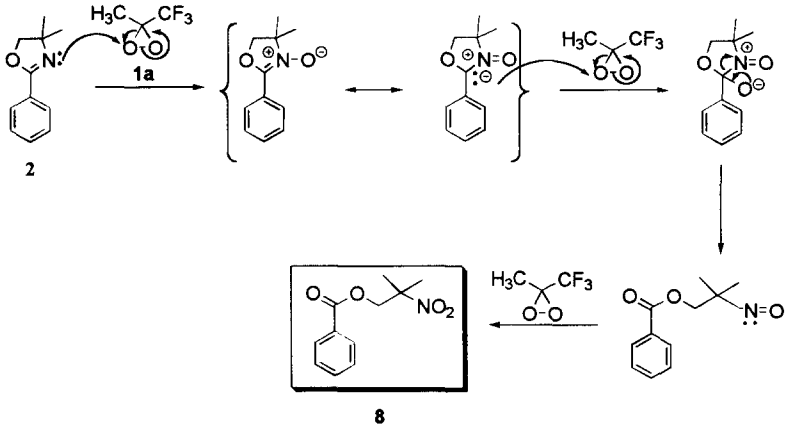
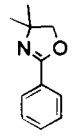
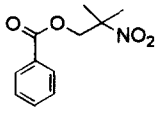
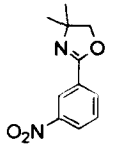
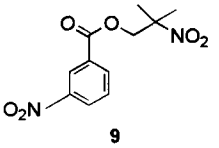
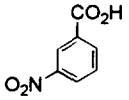
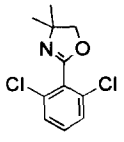
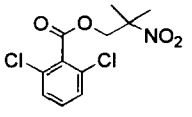
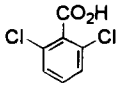
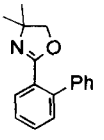
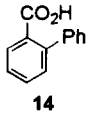
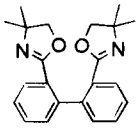
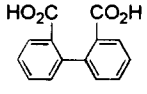
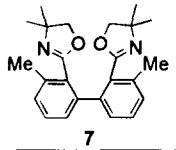
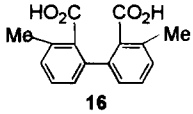


Table 1 summarizes the results for oxidative cleavage of oxazolines **2**–**7** to benzoic acids **11**–**16**. It is important to note that even the hindered oxazoline **7** can be cleaved smoothly to afford 3,3'-dimethyl-2,2'-diphenic acid **16** in 80% overall yield (entry 6) whereas the four aforementioned methods failed.

In conclusion, the dioxirane mediated ring opening reaction followed by mild basic hydrolysis constitutes a "one-pot" method[9] for preparation of substituted benzoic acids from aryl oxazolines.

Table 1. Oxidative Cleavage[a] of Oxazolines

entry	oxazoline	intermediate ester[b]	hydrolysis conditions[c]	acid	yield (%)[d]
1	 **2**	 **8**	5% NaOH, MeOH, 100 °C, 12 h	 **11**	91
2	 **3**	 **9**	5% NaOH, MeOH, 100 °C, 12 h	 **12**	88
3	 **4**	 **10**	5% NaOH, MeOH, 100 °C, 12 h	 **13**	90
4	 **5**	–[e]	5% NaOH, MeOH, 100 °C, 12 h	 **14**	95
5	 **6**	–[e]	10% NaOH, MeOH, 100 °C, 12 h	 **15**	90
6	 **7**	–[e]	30% NaOH, MeOH, 100 °C, 12 h	 **16**	80

[a] Oxidative cleavage conditions: room temperature, 0.1 mmol of substrate, 0.2 mL of 1,1,1-trifluoroacetone, 3.0 mmol of Oxone®, 9.3 mmol of $NaHCO_3$, 1.5 mL of CH_3CN, 1.0 mL of aqueous Na_2•EDTA solution (4×10^{-4} M). [b] Intermediate ester was isolated and characterized by ^1H, ^{13}C NMR, DEPT, IR, LRMS and HRMS. [c] 3 mL of NaOH (concentration as stated above), and 1 mL of MeOH. [d] Isolated yield. [e] Intermediate was not isolated but directly subjected to basic hydrolysis.

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References and Notes

1. For excellent reviews on oxazoline chemistry, see: (a) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837. (b) Gant , T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.
2. For examples of electrophilic substitution of aryl oxazolines, see: (a) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 3158. (b) Meyers, A. I.; Lutomski, K. *J. Org. Chem.* **1979**, *44*, 4465. For examples of nucleophilic substitution of aryl oxazolines, see: (c) Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383. (d) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.
3. Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270.
4. Levin, J. I.; Weinreb, S. M. *Tetrahedron Lett.* **1982**, *23*, 2347.
5. Phillion, D. P.; Pratt, J. K. *Syn. Commun.* **1992**, 13.
6. Oxazolines **2**–**6** were prepared according to the literature procedure, see: Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787. Oxazoline **7** was prepared by dilithiation of **6** using 3 equivalents of *sec*-BuLi/TMEDA in THF at −78 °C for 1.5 h, and quenching with 4 equivalents of methyl iodide at −78 °C followed by warming to rt.
   Selected analytical data for compounds **6** and **7**:
   6: m.p. 138–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.6 Hz, 1.3 Hz, 2H), 7.64–7.26 (m, 6H), 3.75 (d, J = 7.5 Hz, 2H), 3.71 (d, J = 7.5 Hz, 2H), 1.26 (s, 6H), 1.19 (s, 6H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 163.17, 141.39, 129.97, 129.88, 129.50, 127.88, 127.01, 79.33, 67.21, 28.04, 27.93; IR (CCl_4) 2977, 2936, 1641, 1460, 1438, 1425, 1382, 1291 cm^{-1}; EIMS (20 eV) *m/z* 348 (6), 250 (100).
   7: m.p. 165–166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.15 (m, 6H), 3.87 (d, J = 8 Hz, 2H), 3.62 (d, J = 8 Hz, 2H), 2.42 (s, 6H), 1.18 (s, 12H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 161.63, 140.38, 137.12, 128.98, 128.53, 128.38, 127.39, 78.88, 67.66, 28.11, 27.86, 19.88; IR (CH_2Cl_2) 2971, 1663, 1460, 1368, 1346, 1295 cm^{-1}; HRMS for $C_{24}H_{28}N_2O_2$ (M^+), calcd 376.2151, found 376.2147; EIMS (20 eV) *m/z* 376 (100), 304 (56), 232 (13).
7. For epoxidation of olefins using methyl(trifluoromethyl)dioxirane generated *in situ*, see: Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887.
8. (a) Murray, R. W.; Jeyaraman, R.; Pillay, M. K. *J. Org. Chem.* **1987**, *52*, 746. (b) Altamura, A.; Curci, R.; Edwards, J. O. *J. Org. Chem.* **1993**, *58*, 7289.
9. General procedure for hydrolysis of oxazolines: To an acetonitrile solution (1.5 mL) of oxazoline **2** (17.5 mg, 0.1 mmol) was added an aqueous Na_2•EDTA solution (1 mL, 4 × 10^{-4} M), followed by addition of 1,1,1-trifluoroacetone **1** (2.2 mmol, 0.2 mL) via a pre-cooled syringe. To this solution at rt was added in portions a mixture of sodium bicarbonate (0.78 g, 9.3 mmol) and Oxone® (1.84 g, 3 mmol) over a period of 25 min (pH 7–7.5). The reaction was complete in 30 min as shown by TLC. The reaction mixture was poured into water (20 mL), extracted with CH_2Cl_2 (3 × 20 mL), and dried with anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was shown to be the nitroester **8** (21.8 mg, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 4.64 (s, 2H), 1.71 (s, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 165.62, 133.55, 129.74, 129.04, 128.55, 86.35, 68.68, 23.20; IR (CCl_4) 2991, 2949, 1733, 1550, 1453, 1373, 1347, 1270, 1178, 1110, 1071, 1029 cm^{-1}; HRMS for $C_{11}H_{13}NO_4$ (M^+), calcd 223.0845, found 223.0847; EIMS (20 eV) *m/z* 223 (M^+, 7), 177 (23), 106 (7), 105 (100).
   To a methanol solution (1 mL) of nitroester **8** (21.8 mg, 0.099 mmol) was added 5% sodium hydroxide solution (3 mL). The reaction mixture was refluxed for 15 h. After dilution with water (20 mL), the solution was washed with CH_2Cl_2 (10 mL). The aqueous layer was acidified by 2 N HCl to pH 2, and then extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhydrous $MgSO_4$. After evaporation of solvents under reduced pressure, a white solid of benzoic acid **11** (11.1 mg, 91% overall yield) was obtained. The spectroscopic data were identical with those reported in the Aldrich NMR Library.
   Selected analytical data for compounds **9**, **10** and **16**:
   9: ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.81 (t, J = 1.9 Hz, 1H), 8.45 (ddd, J = 8.2 Hz, 2.5 Hz, 1.1 Hz, 1H), 8.29 (dt, J = 8.0 Hz, 1.4 Hz, 1H), 7.68 (t, J = 8.0 Hz, 1H), 4.72 (s, 2H), 1.74 (s, 6H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 163.59, 148.38, 135.26, 130.83, 129.93, 127.97, 124.75, 86.12, 69.31, 23.21; IR (CCl_4) 2995, 1741, 1552, 1540, 1374, 1350, 1293, 1284, 1259, 1130 cm^{-1}; EIMS (20 eV) *m/z* 222 ($M^+ - NO_2$, 27), 150 (100).
   10: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.28 (m, 3H), 4.72 (s, 2H), 1.71 (s, 6H); ^{13}C NMR (67.94 MHz, $CDCl_3$) δ 163.95, 132.63, 131.96, 131.30, 127.94, 85.88, 69.57, 23.31; IR (CCl_4) 2994, 1757, 1552, 1435, 1373, 1347, 1261, 1197, 1141, 1086, 1058 cm^{-1}; HRMS for $C_{11}H_{11}NCl_2O_4$ (M^+), calcd 291.0065, found 291.0068.
   16: ^{1}H NMR (300 MHz, d_6-DMSO) δ 12.50 (br s, 2H), 7.33–7.24 (m, 4H), 7.08 (d, J = 7.1 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (67.94 MHz, d_6-DMSO) δ 169.76, 137.34, 134.65, 133.88, 129.02, 128.01, 126.99, 19.41; EIMS (20 eV) *m/z* 252 ($M^+ - H_2O$, 9), 208 (100), 178 (9), 165 (26), 125 (12), 111 (20), 109 (12), 97 (28), 95 (17), 85 (19), 83 (21), 71 (24), 69 (22).

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