USE OF BARIUM MANGANATE FOR THIAZOLINES AND OXAZOLINES OXIDATION

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ABSTRACT

Oxidation of 2,4-disubstituted thiazolines and oxazolines using $BaMnO_4$ can be carried out to give the corresponding thiazoles and oxazoles. The scope and limitation of this new methodology is discussed.

Keywords: thiazoline/thiazoles, oxazoline/oxazoles, barium manganate, Deoxo-Fluor.

RESUMEN

La oxidación de tiazolinas y oxazolinas 2,4-disustituidas puede ser llevada a cabo utilizando $BaMnO_4$ generando tiazoles y oxazoles respectivamente. El alcance y las limitaciones de esta nueva metodología es discutida.

Palabras clave: tiazolina/tiazol, oxazolina/oxazol, manganato de bario, Deoxo-Fluor.

INTRODUCTION

Oxazole and thiazole rings are an important class of heterocycles found in numerous natural products and pharmaceuticals.[1] One broad approach to oxazole/thiazole synthesis is the oxazoline/thiazoline oxidation (Figure 1). Even though several reagents are reported to perform this transformation, particularly if the heterocycle is activated with an electron-withdrawing group at the 4 or 5 position (where R^2 = CO_2R, Ph, etc), a general and high-yielding method for oxidation of unactivated oxazolines and thiazolines (where R^2 = H or alkyl) has not been described yet.[2]

Metal based oxidation is a common method to dehydrogenate thiazolines and oxazolines. The most important examples are summarized next:

i) NiO_2 oxidation is one of oldest used methodology,[3] and it is useful for activated and unactivated heterocycles. However, the yields are erratic and few oxidation examples of unactivated thiazolines or oxazolines are reported in literature.[4]

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ii) Activated MnO_2 is useful to oxidize activated thiazolines,[5] but this reagent is not frequently used in the oxidation of oxazolines.[6] From a mechanistic perspective NiO_2 and MnO_2 seem to be involved in radical pathways.[7]

iii) More recent methods employing copper salts like $CuBr_2$/DBU/HMTA,[8] CuBr/$Cu(OAc)_2$/Ph(CO)OO*t*Bu,[9] or $CuBr_2$/LiBr/$CaCO_3$,[10] have been reported to oxidize thiazolines and oxazolines.

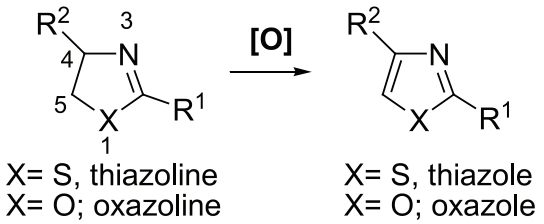


Figura 1

Barium manganate ($BaMnO_4$) is a mild oxidizing reagent used in organic synthesis.[11] It has been applied in many organic transformation like: alcohol oxidation,[12] 1,4-dihydropyridine aromatization,[13] imidazoline oxidation,[14] and oxidative coupling of thiols.[15] Applications of $BaMnO_4$ are similar to the closely related oxide MnO_2, probably because the standard reduction potentials of MnO_4^{2-} and MnO_2 are quite similar.[16] $BaMnO_4$ is a metal oxide that does not need to be activated, like it happens with MnO_2 oxide.[12]

Embarked on a program toward the synthesis of bioactive natural product analogs, containing thiazole and oxazole heterocycles,[17] we are interested in developing new methods for the synthesis of 1,3-thiaza or 1,3-oxoaza five member rings. In this paper we present a new use of $BaMnO_4$ as a reagent able to oxidize activated thiazoline and oxazoline to the corresponding aromatic heterocycles.

MATERIALS AND METHODS

Reactions were monitored by analytical thin layer chromatography (TLC) 0.25 mm Silica gel plastic sheets (Macherey-Nagel, Polygram® SIL G/UV 254). Flash chromatography on Silica gel 60 (J. T. Baker, 40 μm average particle diameter) was used to purify the crude reaction mixtures. NMR spectra were recorded at 400 MHz 100 MHz (^{1}H-NMR, ^{13}C-NMR) using a Bruker ADVANCE at 21 ^{0}C. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity, coupling constant and integration. IR spectra were obtained on a Perkin Elmer 1310 and FTIR 8101A Shimadzu spectrometer, units cm^{-1}. Low-resolution mass spectra were measured on a GCMS Shimadzu QP 1100-EX spectrometer. Elemental analyses were obtained from *vacuum* dried samples and performed on a Fisons EA 1108 CHN-O analyzer. Melting points were determined using a Laboratory Devices Gallenkamp apparatus. All solvents were purified according to literature procedures. All reactions were carried out in dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. Yields are reported for chromatographic and spectroscopic (^{1}H and ^{13}C-NMR) pure compounds unless otherwise stated.

$BaMnO_4$ was prepared according to the literature.[12]

Thioamides **1a**, **1b**, **1c**, **1d** were prepared using Lawesson reagent starting from the corresponding TBS-protected *N*-acylamides, as is described in literature,[18] followed by deprotection with TBAF.

Typical procedure for Deoxo-Fluor cyclodehydration:[19]
Methyl (*R*)-2-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1,3-thiazole-4-carboxylate (2a). To a stirred solution of methyl (S)-3-hydroxy-2-[(3,4,5-trimethoxybenzothioyl)amino]propanoate (**1a**) (50 mg, 0.16 mmol) in CH_2Cl_2 (3 mL) cooled to -20°C (bath temperature) was added dropwise

Deoxo-Fluor reagent (33 μL, 0.18 mmol). The mixture was stirred until all starting material had been consumed (c.a. 1 h). The mixture was quenched with saturated aqueous sodium bicarbonate at –20°C. After warming to room temperature the mixture was further diluted with saturated aqueous sodium bicarbonate and extracted with CH_2Cl_2. The combined organic layers were concentrated at reduced pressure and purified by chromatography (SiO_2, EtOAc/*n*-hexane 1:4) to give thiazoline **2a** (45 mg, 93 %) as a solid: MP 88.5-89.5 °C; IR (KBr) 3569, 1750, 1734, 1458, 1333, 1126, 997, 839; ^{1}H-NMR ($CDCl_3$) δ 3.62 (dd, *J* = 9.3, 11.2 Hz, 1 H), 3.70 (dd, *J* = 8.7, 11.2 *Hz*, 1 H), 3.82 (s, 3 H), 3.87 (s, 3 H), 3.89 (s, 6 H), 5.26, (m, 1 H), 7.10 (s, 2 H); ^{13}C-NMR ($CDCl_3$) δ 35.97, 53.08, 56.72, 61.28, 78.83, 106.42, 128.46, 141.63, 153.46, 170.99, 171.62; EIMS (70 eV), *m/z* (%) 311 ([M$^+$], 29.2), 252 (100.0), 59 8 (16.7); anal. calcd. for C_{14} $H_{17}N$ O_5S: C 54.00, H 5.50, N 4.50, found: C 53.63, H 5.19, N 4.66.

***tert*-butyl (4*S*)-4-[(4*R*)-4-(methoxycarbonyl)-4,5-dihydro-1,3-thiazol-2-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (2b).** Typical procedure for Deoxo-Fluor cyclodehydration was followed using thioamide **1b**, to give thiazoline **2b** (97 % yield) as a solid: MP 79-80 °C; IR (KBr) 1746, 1707, 1377, 1369, 1091, 851; ^{1}H-NMR ($CDCl_3$) δ 1.44 (s), 1.54 (s), 1.60* (bs), 1.70* (bs), 1.75 (s), 3.53 (m, 1 H), 3.63 (m, 1 H), 3.82 (s, 3 H), 4.12 (m, 2 H), 4.80 (m, 1 H), 4.91* (m, 1 H), 5.15 (dd, *J* = 9.4, 9.5 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ 23.71, 24.76,* 28.64, 34.87, 53.06, 59.87, 68.25*, 68.38, 78.98, 81.17, 95.69, 151.90, 171.23, 178.50, * denotes minor conformer peak; EIMS (70 eV), m/z (%) 344 ([M$^+$] 0.4), 329 (20.5), 229 (100.0), 199 (16.1), 57 (76.7); anal. calcd. for C_{15} $H_{24}N_2$ O_5S: C 52.31, H 7.02, N 8.13; found: C 51.97, H 7.45, N 7.59.

Methyl (*R*)-2-neopentyl-4,5-dihydro-1,3-thiazole-4-carboxylate (2c). Typical procedure for Deoxo-Fluor cyclodehydration was followed using thioamide **1c**, to give thiazoline **2c** (85 % yield) as an oil: ^{1}H-NMR ($CDCl_3$) δ 1.05 (s, 9 H), 2.50 (s, 2 H), 3.52 (dd, *J* = 11.1, 9.6 Hz, 1 H), 3.60 (dd, *J* = 11.1, 8.4 Hz, 1 H), 3.81 (s, 3 H), 5.11 (m, 1 H).

Methyl (*R*)-2-(1,1-dimethyl-2-oxopropyl)-4,5-dihydro-1,3-thiazole-4-carboxylate (2d). Typical procedure for Deoxo-Fluor cyclodehydration was followed using thioamide 1d, to give thiazoline **2d** (80 % yield) as an oil: ^{1}H-NMR (CDC_{l3}) δ 1.43 (s, 3 H), 1.44 (s, 3 H), 2.20 (s, 3 H), 3.52 (dd, *J* = 11.3, 9.6 Hz, 1 H), 3.59 (dd, *J* = 11.3, 8.6 Hz, 1 H), 3.59 (s, 3 H), 5.11 (m, 1 H); ^{13}C-NMR (CDC_{l3}) δ 24.25, 25.76, 36.05, 53.00, 54.97, 78.18, 171.44, 178.50, 207.16; EIMS (20eV), m/z (%) 230 ([M$^+$+1], 10.1), 216 (71.2), 187 (41.2), 128 (100).

Typical procedure for $BaMnO_4$ thiazoline oxidation:

Methyl 2-(3,4,5-trimethoxyphenyl)-1,3-thiazole-4-carboxylate (3a). To a stirred solution of compound **2a** (20 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) was added $BaMnO_4$ (214 mg, 0.61 mmol) and refluxed until starting material was consumed, c.a. 6 h. The reaction mixture was cooled, filtered through celite and concentrated at reduced pressure. Purification by chromatography (n-hexanes/EtOAc 3:1) give thiazole **3a** (15 mg, 76%) as a solid: MP 99-100 °C; IR (KBr) 3029, 1752, 1458, 1333, 1129; ^{1}H-NMR (CDC_{l3}) δ 3.91 (s, 3 H), 3.95 (s, 6 H), 3.99 (s, 3 H), 7.28 (s, 2 H), 8.16 (s, 1 H); ^{13}C-NMR ($CDCl_3$) δ 52.81, 56.83, 61.36, 104.82, 127.49, 128.64, 140.99, 147.98, 154.02, 162.27, 169.26. EIMS (70 eV), *m/z* (%) 309 ([M$^+$], 1.2), 278 (14.3) 250 (100.0); anal. calcd. for $C_{14}H_{15}NO_5S$, C 54.36, H 4.89, N 4.53, O 25.86, S 10.37, found: C 54.69, H 5.19, N 3.99, S 10.91.

***tert*-butyl (S)-4-[4-(methoxycarbonyl)-1,3-thiazol-2-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (3b).** Typical proce-

dure for $BaMnO_4$ thiazoline oxidation was followed using thiazoline **2b**, after 3 hours at reflux to give thiazole **3b** (83% yield) as a solid: MP 115-116 ^{0}C; ^{1}H-NMR ($CDCl_3$) δ 1.29 (bs, 6 H), 1.53* (s, 3 H), 1.60 (bs, 6 H), 1.81* (s, 3H), 3.96 (s, 3 H), 4.13-4.19 (m, 1 H), 4.31 (dd, *J* = 6.2 and 9.2 Hz, 1H), 5.28 (m, 1 H), 5.31 (m, 1 H), 8.13 (bs, 1 H); ^{13}C-NMR ($CDCl_3$) δ 23.18, 24.36, 28.62, 52.80, 52.70, 59.89, 69.71, 81.40, 81.89*, 95.71, 127.70, 147.23, 151.89*, 162.18, 175.90, * Denotes minor conformer peaks; EIMS (70 eV), m/z (%) 342 ([M$^+$], 1.5), 241 (2.1), 284 (11.2), 157 (100); anal. calcd. for $C_{15}H_{22}N_2O_5S$ C 52.62, H 6.48, N 8.18, O 23.36, S 9.36, found C 51.99, H 6.98, N 8.78, S 8.79.

Methyl 2-(2,2-dimethylpropyl)-1,3-thiazole-4-carboxylate (3c). Typical procedure for $BaMnO_4$ thiazoline oxidation was followed using thiazoline **2c**, after 3 hours at reflux to give thiazole **3c** (79 % yield) as a white solid: MP 57-58 ^{0}C; IR (KBr) 1748, 1616, 1119; ^{1}H-NMR ($CDCl_3$) δ 1.03 (s, 9H), 2.98 (s, 2H), 3.94 (s, 3 H), 8.08 (s, 1 H); ^{13}C-NMR ($CDCl_3$) δ 29.76, 32.08, 47.48, 52.70, 127.76, 146.81, 162.42, 169.33; EIMS (70 eV), m/z (%) 198 ([M$^+$-CH_3], 5.0), 182 (4.5), 166 (15.2), 157 (100); anal. calcd. for $C_{10}H_{15}NO_2S$ C 56.31, H 7.09, N 6.57, S 15.03 found: C 57.01, H 6.79, N 6.97, S 15.73.

Methyl 2-(1,1-dimethyl-2-oxopropyl)-1,3-thiazole-4-carboxylate (3d). Typical procedure for $BaMnO_4$ thiazoline oxidation was followed using thiazoline **2d**, after 2 hours at reflux, to give thiazole **3d** (70 % yield) as a solid:^{1}H-NMR ($CDCl_3$) δ 1.68 (s, 6 H), 2.14 (s, 3 H), 3.94 (s, 3 H), 8.16 (s, 1 H); ^{13}C-NMR ($CDCl_3$) δ 25.86, 26.01, 52.76, 54.40, 128.34, 147.20, 162.20, 175.16, 207.70 according to reference.[20]

Methyl (1*S*,4*S*)-2-{1-[(*tert*-butoxycarbonyl)amino]-3-methylbutyl}-4,5-dihydro-1,3-oxazole-4-carboxylate (5g). Typical Deoxo-Fluor cyclodehydration procedure was followed using amide **4g**, to give oxazoline **5g** (62 % yield) as a solid: MP 98-99 °C, ^{1}H-NMR ($CDCl_3$) δ 0.95 (d, *J* = 6.6 Hz, 3 H), 0.96 (d, *J* = 6.4 Hz, 3 H), 1.46 (s, 9 H), 1.50-1.78 (m, 3 H), 3.80 (s, 3 H), 4.42-4.60 (m, 3 H), 4.76 (dd, *J* = 7.7, 10.9 Hz,1 H), 5.02 (bs, 1 H); ^{13}C-NMR ($CDCl_3$) δ 22.18, 22.48, 23.03, 28.60, 43.24, 47.83, 53.03, 68.30, 70.36, 80.18, 155.53, 171.19, 171.66.

Procedure for $(NH_4)_6MoO_{24}.4H_2O$ cyclodehydration:[21]

Methyl (*S*)-2-(4-chlorophenyl)-4,5-dihydro-1,3-oxazole-4-carboxylate (5h). To a stirred solution of compound **4h** (130 mg, 0.505 mmol) in dry toluene (35 mL) $(NH_4)_6Mo_7O_{24}.4H_2O$ (135 mg, 0.109 mmol) was added, and refluxed using Dean Stark for 4.30 h. The solvent was evaporated at reduced pressure, and the residue was purified by chromatography (SiO_2, *n*-hexane/EtOAc 2:1) to give compound **5h** (24 mg, 20% yield) as a white solid: MP 87-88°C; ^{1}H-NMR ($CDCl_3$) δ 3.85 (s, 3 H), 4.62 (dd, *J* =1.8, 8.5 Hz, 1 H), 4.72 (t, *J* = 8.5 Hz, 1 H), 4.97 (dd, *J* = 2.6, 8.5 Hz, 1 H), 7.42 (dd, *J* = 1.9, 4.9 Hz, 2 H), 7.95 (dd, *J* = 1.9, 4.9 Hz, 2 H); ^{13}C-NMR (CDC^{13}) δ 53.20, 68.21, 69.98, 128.60, 128.91, 130.63, 131.42, 134.03, 136.97, 169.35, 172.78.

Methyl (*S*)-2-[2-(1*H*-indol-2-yl)ethyl]-4,5-dihydro-1,3-oxazole-4-carboxylate (5f). Typical $(NH_4)_6Mo_7O_{24}.4H_2O$ cyclodehydration procedure was followed using amide **4f**, to give oxazoline **5f** (35% yield) as an oil: ^{1}H-NMR ($CDCl_3$) δ 2.74-2.78 (m, 2 H), 3.14-3.18 (m, 2 H), 3.81 (s, 3 H), 4.42 (t, *J* = 9.7 Hz, 1 H), 4.52 (t, *J* = 8.3 Hz, 1 H), 4.76 (t, *J* = 9.2 Hz, 1 H), 7.06 (d, *J* = 2.1 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.21 (t, *J* = 7.3 Hz, 1 H), 7.37 (d, *J* = 8.1 Hz, 1 H), 7.62 (d, *J* = 7.9 Hz, 1 H), 8.33 (s, 1 H); ^{13}C-NMR ($CDCl_3$) δ 24.98, 36.32, 53.28, 70.16, 71.31, 111.56, 113.19, 120.91, 121.32, 122.39, 127.65, 133.01, 135.29, 171.73, 173.49.

Typical procedure for $BaMnO_4$ oxazoline oxidation:

Methyl 2-(4-chlorophenyl)-1,3-oxazole-4-carboxylate (6h). To a stirred solution of compound **5h** (24 mg, 0.10 mmol) in dry PhMe (3 mL), was added $BaMnO_4$ (88.9 mg, 0.347 mmol) and refluxed for 5 hours. The mixture was filtrated through celite and washed with EtOAc. The solvent was evaporated at reduced pressure, and the residue was purified by chromatography (SiO_2, *n*-Hexane/EtOAc 5:1) to give by-product **7** (26%) and compound **6h** (13.7 mg, 57 % yield) as a solid: MP 112-113 °C; ^{1}H-NMR ($CDCl_3$) δ 3.98 (s, 3 H); 7.49 (dd, *J* = 1.9, 4.8 Hz, 2 H); 8.08 (dd, *J* = 1.9, 4.8 Hz, 2 H); 8.31 (s, 1 H); ^{13}C-NMR ($CDCl_3$) δ 53.21, 122.9, 124.32, 123.7, 127.9, 131.0, 134.8, 135.9, 141.3, 159.9, 167.9; EIMS (70 eV) (m/z) 239 (M^+, 2.5), 241,03 ([M^++2], 0.7), 202 (12,1), 208 (100); anal. calcd. for $C_{11}H_8ClNO_3$ C 55.60, H 3.39, Cl 14.92, N 5.89, O 20.20, found: C, 55.09, H 3.89, C 14.53, N 5.24.

Methyl (*S*)-2-{1-[(*tert*-butoxycarbo-nyl)amino]-3-methylbutyl}-1,3-oxazole-4-carboxylate (6g). Typical procedure for $BaMnO_4$ oxazoline oxidation was followed using oxazoline **5g**, to give oxazole **6g** (25% yield) as an oil and recovered starting material **5g** (26%). **6g**: ^{1}H-NMR ($CDCl_3$) δ 0.95 (d, *J* = 6.4 Hz, 3 H), 0.96 (d, J = 6.5 Hz, 3 H), 1.44 (s, 9 H), 1.61-1.82 (m, 3 H), 3.92 (s, 3 H), 4.95-5.06 (m, 1 H), 5.08 (bs, 1H), 8.18 (s, 1 H); ^{13}C-NMR ($CDCl_3$) δ 22.4; 22.9; 28.6; 43.8; 47.7; 52.5, 80.5; 133.7; 144.1; 155.4; 161.9; 166.4. EIMS (70 eV), m/z (%) 312 ([M^+], 1.5), 281 (10.5), 166 (15.2), 157 (100.0); anal. calcd. for C_{15} $H_{24}N_2$ O_5: C 57.68, H 7.74, N 8.97, 25.61, found: C 57.09, H 8.09, N 9.12 O 25.70.

Ethyl (*R*)-2-oxo-1,3-thiazolidine-4-carboxylate (8).[22] Synthesized according to the literature: ^{1}H- NMR ($CDCl_3$) δ 1.32 (t, *J* = 7.0 Hz, 3 H), 3.62 (dd, *J* = 12.0, 6.0 Hz, 1 H), 3.72 (dd, *J* = 12.0, 7.0 Hz, 1 H), 4.28 (q, *J* = 7.0 Hz, 2 H), 4.46 (dd, *J* = 7.0, 6.0 Hz, 1 H), 7.12 (bs, 1 H).

Methyl (*RS*)-(2-methyl-4,5-dihydro-1,3-oxazol-5-yl)acetate (9). Synthesized according to the literature.[17b] Typical Deoxo-Fluor cyclodehydration procedure was followed using methyl 4-acetamido-3-hydroxybutanoate, to give oxazoline **8** (84 % yield) as an oil: ^{1}H-NMR ($CDCl_3$) δ 1.92 (d, *J* = 1.3 Hz, 3 H), 2.53 (dd, *J* = 6.1, 16.1 Hz, 1 H), 2.70 (dd, *J* = 7.2, 16.1 Hz,1 H), 3.44 (ddd, *J* = 7.1, 14.2, 1.3 Hz,1 H), 3.95 (m, 1 H), 4.84 (m, 1 H); ^{13}C-NMR ($CDCl_3$) δ 14.2, 40.3, 52.1, 60.1, 75.7, 164.9, 170.8.

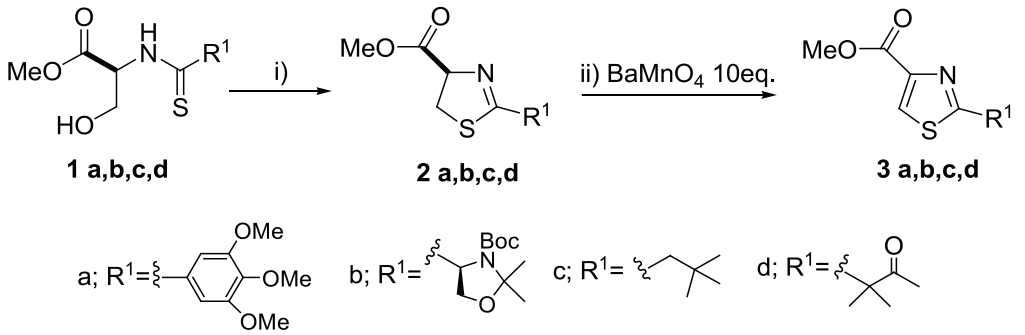
Methyl (*RS*)-2-{[2-(trifluoromethyl)-4,5-dihydro-1,3-thiazol-5-yl]methyl}-1,3-thiazole-4-carboxylate (10).[23b] Synthesized according to literature: ^{1}H-NMR ($CDCl_3$) δ 3.31-3.37 (m, 3 H), 3.96 (s, 3 H), 4.34-4.46 (m, 1 H), 4.48-4.52 (m, 1 H), 8.12 (s, 1 H); ^{13}C-NMR ($CDCl_3$) δ 39.7, 51.9, 52.8, 69.2, 117.3, 128.1, 147.5, 159.7, 161.9, 166.5.

RESULTS AND DISCUSSION

Activated thiazolines were obtained as is depicted in Scheme 1. The L-Serine-thioamides **1a-d**,[18] were cyclodehydrated using [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxo-Fluor) reagent to provide thiazolines **2a-d** in high yields.[19] Thiazolines **2a-d** underwent smooth oxidation to the corresponding thiazole **3a-d** in presence of $BaMnO_4$ (10 eq.), CH_2Cl_2 at reflux, showing good to very good yields (65-83%).

In the context of our studies we compared MnO_2 oxidations,[20] with those obtained using $BaMnO_4$ as oxidant. Preliminary studies have indicated that the reactivity profiles of the two reagents were similar. The results are shown in Table 1, reaction times and yields were comparable, showing similar behavior for the assayed thiazolines. The only advantage for the use of $BaMnO_4$ is the unnecessary previous reagent activation.

Next we investigate the $BaMnO_4$ oxidation for activated oxazolines. The heterocycles were synthesized starting from L-



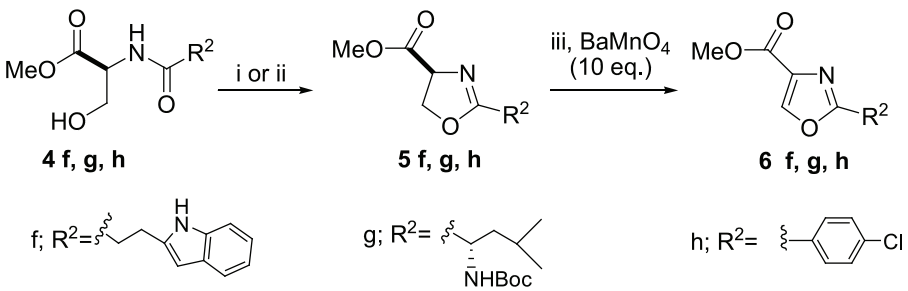
Scheme 1: i) Deoxo-Fluor, -20°C, CH_2Cl_2: **2a** (93%), **2b** (97%), **2c** (85%), **2d** (80%); ii) CH_2Cl_2, reflux: **3a** (76%), **3b** (83%), **3c** (79%), **3d** (65%).

Serine amides **4f-g** using $(NH_4)_6MoO_{24}.4H_2O$ or Deoxo-Fluor cyclodehydration reagents. Cyclization of *N*-acylserines using various molybdenum oxides as catalysts, with azeotropic removal of water, have been described recently by Ishihara and collaborators.[21] When we applied the molybdenum cyclodehydration methodology to amides **4f** and **4h**, the yields were fairly poor, 20% and 35% respectively. Oxazoline **5g** was obtained by cyclodehydration of amide **4g** using Deoxo-Fluor reagent in high yield (82%).[23] Even though Deoxo-Fluor is used in equimolecular amounts and is more expensive than $(NH_4)_6MoO_{24}.4H_2O$, yields are better resulting in a more convenient methodology to synthesize oxazolines.

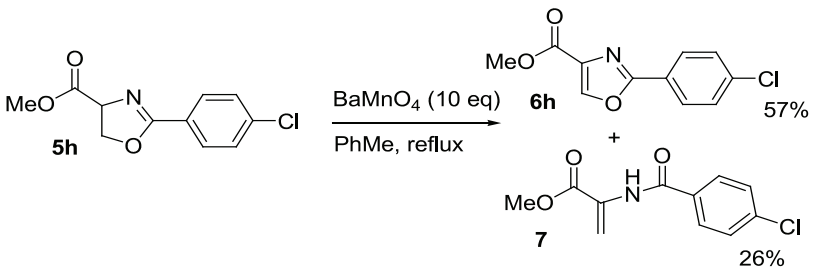
In general, metal oxides like MnO_2 are poor oxidants of oxazolines. Unfortunately $BaMnO_4$ is not an exception. In the assayed conditions: $BaMnO_4$ (10 eq.) in toluene at reflux, oxazolines **5g** and **5h** were partially

			Method		
			MnO_2†	$BaMnO_4$	
Reagent	**Product**	Yield (%)	Time (h)	Yield (%)	Time (h)
2a	**3a**	80	4	76	6
2b	**3b**	79	3	83	3
2c	**3c**	73	3	79	3
2d	**3d**	70	3	65	2

Table 1. Comparison of MnO_2 and $BaMnO_4$ thiazoline oxidation. *† oxidation conditions MnO_2 (10 eq.),CH_2Cl_2 at reflux.*



Scheme 2: i) $(NH_4)_6MoO_{24}.4H_2O$, PhMe, Dean-Stark, reflux: **5f** (20%), **5g** (35%); ii) Deoxo-Fluor, -20 °C, CH_2Cl_2: **5h** (82 %); iii) PhMe reflux: **6f** (0 %) + **5f** (10%), **6g** (30%) + **5g** (23 %), **6h** (26%) + **5h** (23%).



Scheme 3.

transformed to the corresponding oxazoles (Scheme 2). Indolyl-oxazoline **5f** decomposed under the mentioned conditions, probably due to the instability of the starting material. After five hours at reflux we recovered starting material **5f** (10%) and decomposition products. Oxazoline **5g** was partially transformed, after refluxing for 6 hours, into the desired oxazole **6g** with 30% yield, recovering the starting material **5g** 23% yield. Compound **5h** gave the desired oxazole **6h** (57%) but also the by product **7** (26%), see Scheme 3.

As is reported in literature, MnO_2 oxidation of oxazoline is more difficult than it is for thiazoline,[2] and the same behavior occurs when we used $BaMnO_4$ in the assayed conditions. The harsher conditions involving higher temperature and reaction times seemed to promote diverse side reactions.

We also evaluated the ability of $BaMnO_4$ to oxidize unactivated substrates like thiazolidin-2-one **8**, 2,5-disubstituted 2-oxazoline **9** and 2,5-disubstituted 2-oxazoline 10, see Figure 2. Under standard conditions, CH_2Cl_2 or PhMe at reflux, **10** eq. $BaMnO_4$, we were not able to obtain the desired aromatic product.

Attempts to oxidize oxazoline **9**, using Phase Transfer Catalyst conditions (PTC: $BaMnO_4$-Al_2O_3-$CuSO_4.5H_2O$), described by Kim and collaborators,[24] led to the ring opening products and starting material. Thiazolidine **8** was also evaluated using activated MnO_2, particle size <10μ, conditions described by Shioiri and co-workers for thiazolidine oxidation,[25] but the result was unsuccessful.

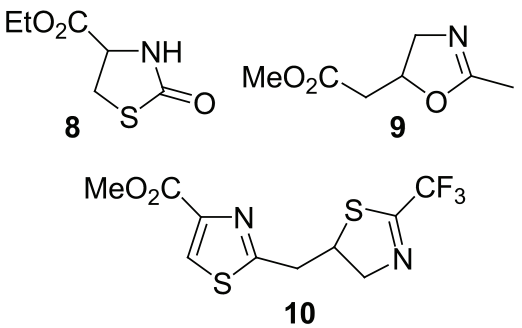


Figure 2: Thiazolidin-2-one (**8**), 2,5-disubstituted 2-oxazoline (**9**) and 2,5-disustituted 2-thiazoline (**10**).

CONCLUSION

In summary a new application of $BaMnO_4$ oxidation reagent for 2,4-disubstituted activated thiazolines and oxazolines has been described. Even though more examples are needed to extend the methodology for thiazolines the obtained yields are good and comparable with those obtained using MnO_2. In addition our methodology has the advantage that it does not need to be activated before use. For oxazoline oxidations the methodology seems to be more limited and the yields are modest.

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REFERENCES

1. Jin, Z. (2006) Imidazole, Oxazole and Thiazole Alkaloids. *Natural Product Report* **23**: 446-496 and references therein.
2. Taylor, E., Wipf, P. (2004) The Chemistry of Heterocyclic Compounds. Oxazoles: Synthesis, reactions and spectroscopy, V 60. Palmer C. D., and Venkatraman, S. Synthesis and Reactions of Oxazoles. Part A, John Wiley & Sons, Inc. Hoboken, New Jersey, 4-16.
3. Evans, D. L., Minster, D. K., Jordis, U., Hecht, S. M., Mazzu, A. L., Meyers, A. I. (1979) Nickel peroxide dehydrogenation of oxygen-, sulfur-, and nitrogen-containing heterocycles. *Journal of Organic Chemistry* **44**: 497-501.
4. Levin, J., Weinreb, S. M. (1983) Total synthesis of eupolauramine. *Journal of the American Chemical Society* **105**: 1397-1398.
5. North, M., Pattenden, G. (1990) Synthetic studies towards cyclic peptides. Concise synthesis of thiazoline and thiazole containing amino acids. *Tetrahedron*, **46**: 8267-8290.
6. Okumura, K., Ito, A., Nakamura, Y., Shin, C. G. (1996) Dehydrooligopeptides. XIV. Syntheses of 2-[(Z)-1-Amino-1-alken-1-yl]oxazole-4-carboxylic Acid and the Main Common Skeleton of Thiostrepton Peptide Antibiotics, A10255 G and J. *Bulletin of the Chemical Society of Japan* **69**: 2309-2316.
7. Fatiadi, A. (1971) Evidence for adsorption as the first step in the solid-state oxidation of benzenehexenol with active manganese dioxide. *Journal of the Chemical Society (C)* 889-892.
8. Barrish, J. C., Singh, J., Spergel, S. H., Han, W-C., Sissik, T. P., Kronenthal, D. R., Muellar, R. H. (1993) Cupric bromide mediated oxidation of 4-carboxyoxazolines to the corresponding oxazoles. *Journal of Organic Chemistry* **58**: 4494-4496.
9. a) Meyers, A. I., Tavares, F. X. (1994) The oxidation of 2-oxazolines to 1,3-oxazoles. *Tetrahedron Letters* **35**: 2481-2484; b) Meyers, A. I., Tavares, F. X. (1996) Oxidation of Oxazolines and Thiazolines to Oxazoles and Thiazoles. Application of the Kharasch-Sosnovsky Reaction. *Journal of Organic Chemistry* **61**: 8207-8215.
10. Klein, R. F. X., Horak, V., Baker, G. A. S. (1993) Novel dehydrogenation of 2,5-diaryl substituted Δ^2-oxazolines to oxazoles. *Collection of Czechoslovak Chemical Communications* **58**: 1631-1635.
11. Hudlicky, M. (1990) *Oxidation in organic chemistry. ACS Monograph 186*, American Chemical Society, Washigton DC.
12. Firouzabadi, H., Ghaderi, E. (1978) Barium manganate. An efficient oxidizing reagent for oxidation of primary and secondary alcohols to carbonyl compounds. *Tetrahedron Letters.* **19**: 839-842.

13. Memarian, H. R., Sadeghi, M., Momeni, A. R. (2001) Aromatization of Hantzsch 1,4-dihydropyridines using barium manganate. *Synthetic Communications* **31**: 2241-2244.
14. Hughey, I., Knapp, S., Harvey, S. (1980) Dehydrogenation of 2-Imidazolines to Imidazoles with Barium Manganate. *Synthesis* 489-492.
15. Firouzabadi, H., Abbassi, M. H., Babak, K. (1999) Highly efficient oxidative coupling of thiols by active manganase dioxide (AMD) and barium manganate (BM) under solvent-free conditions at room temperature. *Synthetic Communications* **29**: 2527-2531.
16. Cotton, F.A., Wilkinson, G. (1988) Advanced Inorganic Chemistry, 5th edition, John Wiley & Sons, New York, USA,
17. a) Mahler, G., Serra, G., Dematteis, S., Saldaña, J., Domínguez, L., Manta, E. (2006) Synthesis and biological evaluation of simplified mycothiazole analogues. *Bioorganic & Medicinal Chemistry Letters* **16**: 1309-1311; b) Sellanes, D., Scarone, L., Mahler, G., Manta, E., Baz, A., Dematteis, S., Saldaña, J., Domínguez, L., Wipf, P., Serra, G. (2006) Synthesis and Evaluation of Anthelmintic and Cytotoxic Properties of Bis-1,3-Azole Analogs of Natural Products. *Letters in Drugs Design and Discovery* **3**: 625-632.
18. Pedersen, B. S., Scheibye, S., Clausen, K., Lawesson, S.–O. (1978) The dimmer of p-methoxy phenylthionophosphine sulfide as thiation reagent. A new route to o-substituted thioesters and dithioesters. *Bulletin des Societés Chimiques Belges* **87**: 293-297.
19. Mahler, G., Serra, G., Antonow, D., Manta, E. (2001) Deoxo-fluor mediated cyclodehydration of β-hydroxy thioamides to the corresponding thiazolines. *Tetrahedron Letters* **42**: 8143-8146.
20. For MnO_2 oxidation of compound **2d** see: Serra, G., Mahler, G., Manta, E. (1998) Preparation of Methyl 2-(1,1-Dimethyl-2-oxopropyl)-thiazole and related 2,4-disubstituted thiazoles. Key intermediates in the synthesis of anthelmintic agents based on marine natural products. *Heterocycles* **48**: 2035-2048.
21. Sakakura, A., Kondo, R., Ishihara, K. (2005) Molybdenum Oxides as Highly Effective Dehydrative Cyclization Catalysts for the Synthesis of Oxazolines and Thiazolines. *Organic Letters* **7**: 1971-1974.
22. Synthesized according literature procedures: Kubodera, N., Nagano, H., Takagi, M., Matsunaga, Y. (1982) *Heterocycles* **18**: 259-263.
23. (a) Phillips, A. J., Uto, Y., Wipf, P., Reno, M., Williams D. (2000) Synthesis of functionalized oxazolines and oxazoles with DAST and Deoxo-Fluor. *Organic Letters* **2**: 1165-1168; (b) Scarone, L., Sellanes, D., Manta, E., Wipf, P., Serra, G. (2004) Use of Deoxo-Fluor for double cyclization to bis-thiazolines. Limitations of this agent for the synthesis of oxazolines. *Heterocycles* **63**: 773-775.
24. Kim, K. S., Chung, S., Cho, I., Hahn, C. S. (1989) Selective oxidation of alcohol by manganates. *Tetrahedron Letters* **30**: 2559-2562
25. For the synthesis of activated thiazolidines see: Sugiyama, H., Yokokawa, F., Shioiri, T. (2003) Total synthesis of mycothiazole, a polyketide heterocycle from marine sponges. *Tetrahedron* **59**: 6579-6586.