USE OF BARIUM MANGANATE FOR THIAZOLINES AND
OXAZOLINES OXIDATION

S. GRACIELA MAHLER*, GLORIA SERRA, IGNACIO VIERA, EDUARDO MANTA.

(RECIBIDO: DICIEMBRE 2007; ACEPTADO ENERO 2008)

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$_2$R, 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.$^4$
ii) Activated MnO₂ is useful to oxidize activated thiazolines,⁵ but this reagent is not frequently used in the oxidation of oxazolines.⁶ From a mechanistic perspective NiO₂ and MnO₂ seem to be involved in radical pathways.⁷

iii) More recent methods employing copper salts like CuBr₂/DBU/HMTA,⁸ CuBr/Cu(OAc)₂/Ph(CO)OttBu,⁹ or CuBr₂/ LiBr/CaCO₃,¹⁰ have been reported to oxidize thiazolines and oxazolines.

**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 (¹H-NMR, ¹³C-NMR) using a Bruker ADVANCE at 21 °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 (¹H and ¹³C-NMR) pure compounds unless otherwise stated.

**Barium manganate** (BaMnO₄) 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 imidazole oxidation,¹⁴ and oxidative coupling of thiols.¹⁵ Applications of BaMnO₄ are similar to the closely related oxide MnO₂, probably because the standard reduction potentials of MnO₄²⁻ and MnO₂ are quite similar.¹⁶ BaMnO₄ is a metal oxide that does not need to be activated, like it happens with MnO₂ 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 BaMnO₄ as a reagent able to oxidize activated thiazoline and oxazoline to the corresponding aromatic heterocycles.

**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-trimethoxybenzo-thioly]amino]propanoate (1a) (50 mg, 0.16 mmol) in CH₂Cl₂ (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 CH₂Cl₂. The combined organic layers were concentrated at reduced pressure and purified by chromatography (SiO₂, 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; ¹H-NMR (CDCl₃) 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); ¹³C-NMR (CDCl₃) δ 35.97, 53.08, 56.72, 78.83, 106.42, 128.46, 141.63, 153.46, 170.99, 171.62; EIMS (70 eV), m/z (%) 331 ([M⁺], 29.2), 252 (100.0), 59.8 (16.7); anal. calcd. for C₁₄H₂₁NO₃S: C 53.63, H 5.19, N 4.66.

**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: ¹H-NMR (CDCl₃) 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); ¹³C-NMR (CDCl₃) 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 BaMnO₄ 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 CH₂Cl₂ (2 mL) was added BaMnO₄ (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) gave thiazole 3a (15 mg, 76%) as a solid: MP 99-100 °C; IR (KBr) 3029, 1752, 1458, 1333, 1129; ¹H-NMR (CDCl₃) δ 3.91 (s, 3 H), 3.95 (s, 6 H), 4.91* (m, 1 H), 5.15 (dd, J = 9.4, 9.5 Hz, 1 H); ¹³C-NMR (CDCl₃) 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 (%) 330 ([M⁺], 0.4), 329 (20.5), 229 (100.0), 199 (16.1), 57 (76.7); anal. calcd. for C₁₅H₂₄N₂O₅S: 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 proce-
Use of Barium Manganate for thiazoline and oxazoline oxidation

Rev. Latinoamer. Quím. 35/3 (2007) 77

dure for BaMnO₄ thiazoline oxidation was followed using thiazoline 2b, after 3 hours at reflux to give thiazole 3b (83% yield) as a solid: MP 115-116 °C; ¹H-NMR (CDCl₃) δ 1.29 (bs, 6 H), 1.53* (s, 3 H), 1.60 (bs, 6 H), 1.81* (s, 3 H), 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); ¹³C-NMR (CDCl₃) δ 23.18, 24.36, 28.62, 52.80, 52.76, 7.68, N 8.18, O 23.36, S 9.36, found: C 51.99, H 6.98, N 6.57, S 15.03.

Methyl 2-(2,2-dimethylpropyl)-1,3-thiazole-4-carboxylate (3c). Typical procedure for BaMnO₄ 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 °C; IR (KBr) 1748, 1616, 1119; ¹H-NMR (CDCl₃) δ 1.03 (s, 9 H), 2.98 (s, 2H), 3.94 (s, 3 H), 8.08 (s, 1 H); ¹³C-NMR (CDCl₃) δ 29.76, 32.08, 47.48, 52.70, 127.76, 146.81, 162.42, 169.33; EIMS (70 eV), m/z (%) 198 ([M’-CH₃], 5.0), 182 (4.5), 166 (15.2), 157 (100); anal. calcd. for C₁₇H₂₂N₂O₅S C 52.62, H 6.48, N 8.18, O 23.36, S 8.97.

Methyl 2-(1,1-dimethyl-2-oxopropyl)-1,3-thiazole-4-carboxylate (3d). Typical procedure for BaMnO₄ thiazoline oxidation was followed using thiazoline 2d, after 2 hours at reflux, to give thiazole 3d (70% yield) as a solid: ¹H-NMR (CDCl₃) δ 1.68 (s, 6 H), 2.14 (s, 3 H), 3.94 (s, 3 H), 8.16 (s, 1 H); ¹³C-NMR (CDCl₃) δ 25.86, 26.01, 52.76, 54.40, 128.34, 147.20, 162.20, 175.16, 207.70 according to reference.²⁰

Methyl (1S,4S)-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 4f, to give oxazole 5g (62% yield) as a solid: MP 98-99 °C; ¹H-NMR (CDCl₃) 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); ¹³C-NMR (CDCl₃) 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 (NH₄)₆MoO₂₄·4H₂O 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) (NH₄)₆MoO₂₄·4H₂O (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 (SiO₂, n-hexane/EtOAc 2:1) to give compound 5h (24 mg, 20% yield) as a white solid: MP 87-88 °C; ¹H-NMR (CDCl₃) δ 3.85 (s, 3 H), 4.72 (dd, J = 2.1, 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); ¹³C-NMR (CDCl₃) 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-(1H-indol-2-yl)ethyl]-4,5-dihydro-1,3-oxazole-4-carboxylate (5f). Typical (NH₄)₆MoO₂₄·4H₂O cyclodehydration procedure was followed using amide 4f, to give oxazole 5f (35% yield) as an oil: ¹H-NMR (CDCl₃) 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); ¹³C-NMR (CDCl₃) 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 BaMnO₄ 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 BaMnO₄ (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 (SiO₂, 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; ¹H-NMR (CDCl₃) 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); ¹³C-NMR (CDCl₃) δ 53.21, 122.9, 124.32, 123.7, 127.9, 131.0, 134.8, 134.5, 141.3, 159.9, 167.9; EIMS (70 eV), m/z (M +, 26%) and compound 6g (26%).

**RESULTS AND DISCUSSION**

Activated thiazolines were obtained as is depicted in Scheme 1. The L-Serine-thioamidates 1a-d,¹⁸ were cyclodehydrated using [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxy-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 BaMnO₄ (10 eq.), CH₂Cl₂ at reflux, showing good to very good yields (65-83%).

In the context of our studies we compared MnO₄ oxidations,²⁰ with those obtained using BaMnO₄ 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 BaMnO₄ is the unnecessary previous reagent activation.

Next we investigate the BaMnO₄ oxidation for activated oxazolines. The heterocycles were synthesized starting from L-
Use of Barium Manganate for thiazoline and oxazoline oxidation

Serine amides 4f-g using (NH₄)₆MoO₂₄·4H₂O 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. 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%).

In general, metal oxides like MnO₂ are poor oxidants of oxazolines. Unfortunately BaMnO₄ is not an exception. In the assayed conditions: BaMnO₄ (10 eq.) in toluene at reflux, oxazolines 5g and 5h were partially

**Table 1.** Comparison of MnO₂ and BaMnO₄ thiazoline oxidation. † oxidation conditions MnO₂ (10 eq.), CH₂Cl₂ at reflux.

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>3a</td>
<td>80</td>
<td>4</td>
<td>76</td>
<td>6</td>
</tr>
<tr>
<td>2b</td>
<td>3b</td>
<td>79</td>
<td>3</td>
<td>83</td>
<td>3</td>
</tr>
<tr>
<td>2c</td>
<td>3c</td>
<td>73</td>
<td>3</td>
<td>79</td>
<td>3</td>
</tr>
<tr>
<td>2d</td>
<td>3d</td>
<td>70</td>
<td>3</td>
<td>65</td>
<td>2</td>
</tr>
</tbody>
</table>

**Scheme 1:** i) Deoxo-Fluor, -20°C, CH₂Cl₂: 2a (93%), 2b (97%), 2c (85%), 2d (80%); ii) CH₂Cl₂, reflux: 3a (76%), 3b (83%), 3c (79%), 3d (65%).

**Scheme 2:** i) (NH₄)₆MoO₂₄·4H₂O, PhMe, Dean-Stark, reflux: 5f (20%), 5g (35%); ii) Deoxo-Fluor, -20 °C, CH₂Cl₂: 5h (82%); iii) PhMe reflux: 6f (0%) + 5f (10%), 6g (30%) + 5g (23%), 6h (26%) + 5h (23%).
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, MnO₂ oxidation of oxazoline is more difficult than it is for thiazoline, and the same behavior occurs when we used BaMnO₄ 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 BaMnO₄ 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, CH₂Cl₂ or PhMe at reflux, 10 eq. BaMnO₄, we were not able to obtain the desired aromatic product.

Attempts to oxidize oxazoline 9, using Phase Transfer Catalyst conditions (PTC: BaMnO₄-Al₂O₃-CuSO₄·5H₂O), described by Kim and collaborators, led to the ring opening products and starting material. Thiazolidine 8 was also evaluated using activated MnO₂, particle size <10μ, conditions described by Shioiri and co-workers for thiazolidine oxidation, but the result was unsuccessful.

As shown in Scheme 3, we also evaluated the ability of BaMnO₄ 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, CH₂Cl₂ or PhMe at reflux, 10 eq. BaMnO₄, we were not able to obtain the desired aromatic product.

Attempts to oxidize oxazoline 9, using Phase Transfer Catalyst conditions (PTC: BaMnO₄-Al₂O₃-CuSO₄·5H₂O), described by Kim and collaborators, led to the ring opening products and starting material. Thiazolidine 8 was also evaluated using activated MnO₂, particle size <10μ, conditions described by Shioiri and co-workers for thiazolidine oxidation, but the result was unsuccessful.
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.

ACKNOWLEDGEMENTS

This work was supported by grants from Dicyt: Fondo Clemente Estable N° 9002 and PEDECIBA-ONU. We would like to thank Horacio Pezaroglo for NMR spectra.

REFERENCES


