Direct oxidation of \( \Delta^2 \)-isoxazolines synthesis by metal ion-mediated diastereoface-selective 1,3-dipolar cycloaddition with “activated” DMSO

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1. Introduction

A large part of the research of stereocontrolled versions of 1,3-dipolar cycloaddition in the last few years dealt with the influence exerted by a stereocentre located in either of the two cycloaddends (Pelissier, 2007; Hiroyuki et al., 2009; Peng et al., 2008). With our efforts to utilize heterocyclic compounds as dipolarophile components in 1,3-dipolar cycloaddition reactions (Ben Hamadi and Msaddek, 2007; Ben Hamadi et al., 2012; Louhichi et al., 2012), we have recently demonstrated that nitrile oxides react with chiral alkene to produce mainly anti-adducts with > 80% \( \pi \)-facial stereoselectivity (Ben Hamadi and Msaddek, 2011). Since Lewis acids are a powerful tool in organic synthesis, one of today’s challenges in the field of 1,3-dipolar reactions is the Lewis acid-induced control of regio- and stereoselectivities in these reactions (Andrei and Peter, 2010). The Lewis acid-catalyzed reaction control of nitrile oxide cycloadditions must be an important research subject (Hidetoshi et al., 2000). Dimethylsulfoxide is widely employed as an oxidant, most notably in the transformation of primary alcohols into aldehydes (Tidwell, 1990). However, many of these methods are subjected to certain drawbacks such as longer reaction times, low yields and toxicity due to the presence of some elements embodied in the reagents utilized. So still there is a need for the development of new catalysts which can overcome all these drawbacks.

Therefore, we report in the present paper the investigation of reactions of chiral dipolarophiles and aromatic nitrile oxide to afford the \( \Delta^2 \)-isoxazole-4,6(5H,6aH)-dione. We show that a swern reaction of 4-hydroxyl-\( \Delta^2 \)-isoxazol-6(6aH)-one derivatives with dimethylsulfoxide and oxalyl chloride under Swern conditions led to a \( \Delta^2 \)-isoxazole-4,6(5H,6aH)-dione.

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2. Results and discussion

The reaction of 5-hydroxy-3-methyl-N-phenyl-1,5-dihydropyrrol-2-one 1 with aromatic nitrile oxide 2 at 110 °C in toluene, without metal ions, gave a mixture of diastereomeric cycloadducts [3].

Lewis acids have been employed successfully as catalysts for 1,3-dipolar cycloaddition reaction between aromatic nitrile oxides and pyrrolidinone 1. Although the reactions also proceeded smoothly in the presence of a Lewis acid (0.5 equiv. to 1), diastereoselectivities of reactions were not improved. Increase in the amount of MgBr₂ to 1 equiv. decreased the selectivity under similar conditions (Table 1). Examination of the electronic nature of benzonitrile oxides and pyrrolidinone 1 was carried out. As shown in Table 1 (Entry 6), the nitrile oxides having an electron-donating substituent showed higher diasteroselectivities.

The synthetic route to the targeted Δ²-isoxazolines 3ae–be is outlined in Scheme 1. In this paper, two synthetic approaches toward the Δ²-isoxazoline system have been reported. The first approach is based on the 1,3-dipolar cycloaddition of 5-hydroxy-4-methyl-1,5-dihydropyrrol-2-ones 1a–b with aromatic nitrile oxides 2c–e at 110 °C in toluene solution for 2 h, compound 3ae–be was obtained. The addition of aromatic nitrile oxides 2 with 5-hydroxy-4-methyl-1,5-dihydropyrrol-2-ones as both a regio and diastereospecific reaction is described. (Scheme 1) The second reaction pathway as shown in Scheme 1, is the reaction between Δ²-isoxazoline derivatives 3ac–be and dimethylsulfoxide under Swern conditions which gave good yields of Δ²-isoxazoline derivatives 5ac–be (Konopikova et al. 1992).

3. Conclusion

In conclusion, we have developed a methodology for the magnesium ion-based stereocontrol of aromatic nitrile oxides with 5-hydroxy-4-methyl-1,5-dihydropyrrol-2-ones. The Swern conditions, involving the use of very simple and inexpensive reagents, allow the one-pot transformation of 4-hydroxy-Δ²-isoxazol-6(6aH)-one with a Δ²-isoxazole-4,6(5H,6aH)-dione into synthetically valuable. These findings constitute a significant addition to the growing list of synthetic applications of activated dimethylsulfoxide.

### Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar¹</th>
<th>Additive (equiv.)</th>
<th>Ratio a anti-3: syn-4</th>
<th>Rdt% b</th>
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<tr>
<td>1</td>
<td>Ph</td>
<td>None</td>
<td>92/8</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>MgBr₂ (0.5 equiv.)</td>
<td>92/8</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>MgBr₂ (1 equiv.)</td>
<td>97/3</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>ZnCl₂ (1 equiv.)</td>
<td>92/8</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>p-C₆H₄CH₃</td>
<td>MgBr₂ (1 equiv.)</td>
<td>95/5</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>p-C₆H₄OCH₃</td>
<td>MgBr₂ (1 equiv.)</td>
<td>100/trace</td>
<td>95</td>
</tr>
</tbody>
</table>

a Determined by ¹H NMR.

b Combined yield after column chromatography.

![Scheme 1](image-url)
4. Experimental details

4.1. General

Infrared spectra were recorded on a Perkin-Elmer IR-197 spectrophotometer in KBr disks. NMR spectra were obtained with a Bruker AC 300 spectrometer operating at 300 MHz for $^1$H and at 75.64 MHz for $^{13}$C using TMS as the internal standard. Elemental analysis was performed with a Perkin-Elmer 240B microanalyzer. The melting points, thermal transitions, and mesomorphic textures were determined using an Olympus BX50 microscope equipped with a Mettler Toledo FP-82 hot-stage and a PM-30 exposure control unit.

4.2. Materials

All the reagents were obtained from commercial sources and used without further purification. 5-Hydroxy-4-methyl-1,3-dihydropyrrol-2-ones 1a–b were obtained by the reduction of citraconimide derivatives with NaBH₄ (Nobuyuki et al., 2002). The organic solvents were of commercial grade quality and all were dried by traditional methods. In general, all the compounds were purified by column chromatography on silica gel (60–120 mesh), and crystallization from analytical grade solvents. The purity of the sample was checked by thin-layer chromatography (Merck Kieselgel 60F254).

4.3. Addition of aromatic nitrile oxides to 5-hydroxy-1,3-dihydropyrrol-2-one derivatives

A solution of dipolarophiles 4a–b (1 mmol), MgBr₂ (x mmol, see Table 1) and chloroformes 2c–e (1.1 mmol) in toluene (10 mL), was stirred at 110 °C. The precipitated triethylammonium chloride was removed by filtration, and the filtrate was concentrated in vacuo, and chromatography (SiO₂: ethyl acetate/petroleum ether, 2:1) afforded compounds 5ac–be.

4.4. Oxidation of isoaxazolines 5ac–be

To a solution of oxalyl chloride (5 equiv) in dry CH₂Cl₂ (10 mL), at −78 °C under an argon atmosphere, was added DMSO (7 equiv). The solution was stirred for 10 min, until effervescence ceased. A solution of the isoaxazolines 3ac–be (1 mmol) in dry CH₂Cl₂ (5 mL) was added dropwise, and the solution was stirred for 10 min at −78 °C. Triethylamine (10 equiv) was then added and the solution was left to warm to 0 °C for 30 min, while stirring. The reaction mixture was diluted with CH₂Cl₂ (20 mL) and washed with saturated aqueous NaHCO₃ (3 × 20 mL). The organic layer was dried (MgSO₄) and evaporated, and the residue was purified by chromatography (SiO₂: ethyl acetate/petroleum ether, 1:4) to afford compounds 5ac–be.

4.4.1. 5-(2,4-dichlorophenyl)-6a-methyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoaxazole-4,6-dione 5ac

Yield (0.244 g, 80%), white solid. M.p. = 197–199 °C. Anal. Calcd. For C₂₀H₁₅N₂O₃: C, 66.35; H, 4.15; N, 7.05%. Found: C, 66.5; H, 4.3; N, 7.1%. 1H NMR (CDCl₃; 300 MHz) δ: 1.87 (s, 3H, CH₃), 3.81 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 4.59 (s, 1H, 3a-H), 7.15–7.18 (d, 2H): AA'BB' part.

4.4.2. 5-(2,4-dimethylphenyl)-6a-methyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoaxazole-4,6-dione 5ad

Yield (0.304 g, 95%), white solid. M.p. = 155–157 °C. Anal. Calcd. For C₂₁H₁₆N₂O₃: C, 71.23; H, 5.04; N, 8.75%. Found: C, 71.12; H, 4.91; N, 8.50%. IR (KBr) υ ~ 1638 (C=O), 3219 (NH). 1H NMR (CDCl₃; 300 MHz) δ: 1.20 (s, 3H, CH₃), 2.01 (s, 3H, CH₃), 3.83 (s, 3H, OCH₃), 7.08 (d, 2H): AA'BB' part.

4.4.3. 5-(2,4-dimethoxyphenyl)-6a-methyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoaxazole-4,6-dione 5ae

Yield (0.285 g, 85%), white solid. M.p. = 222–224 °C. Anal. Calcd. For C₂₃H₂₂N₂O₄: C, 67.84; H, 4.80; N, 8.33%. Found: C, 67.69; H, 4.90; N, 8.30%. IR (KBr) υ ~ 1650 (C=O), 3378 (NH). 1H NMR (DMSO; 300 MHz) δ: 1.75 (s, 3H, CH₃), 3.81 (s, 3H, OCH₃), 5.16 (s, 1H, 3a-H), 7.05 (d, 2H) and 7.89 (d, 2H): AA'BB' part. J ~ 8.7 Hz, 7.30–7.53 (m, 5H, H arom).

4.4.4. 5-(2,4-dimethylphenyl)-6a-methyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoaxazole-4,6-dione 5be

Yield (0.269 g, 80%), white solid. M.p. = 153–155 °C. Anal. Calcd. For C₂₀H₁₆N₂O₃: C, 68.74; H, 4.80; N, 8.33%. Found: C, 67.60; H, 4.75; N, 8.20%. IR (KBr) υ ~ 1634 (C=O), 3192 (NH). 1H NMR (DMSO; 300 MHz) δ: 1.85 (s, 3H, CH₃), 3.81 (s, 3H, OCH₃), 4.58 (s, 1H, 3a-H), 6.99. 7.21 (AA'BB', H arom. = 8.7 Hz), 7.46–8.02 (m, 5H, H arom). 13C{1H}NMR (CDCl₃; 75.47 MHz) δ: 19.24 (CH₃), 55.58 (OCH₃), 59.41 (C-3a), 87.95 (C-5a), 114.55–159.85 (C arom.), 152.77 (C-3), 169.77 (C-4), 173.10 (C-6).

4.4.5. 5-(2,4-dimethoxyphenyl)-6a-methyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoaxazole-4,6-dione 5de

Yield (0.315 g, 90%), white solid. M.p. = 166 °C. Anal. Calcd. For C₂₃H₂₃N₂O₄: C, 68.55; H, 5.19; N, 8.00%. Found: C, 68.40; H, 5.10; N, 8.10%. IR (KBr) υ ~ 1633 (C=O). 1H NMR (CDCl₃; 300 MHz) δ: 1.84 (s, 3H, CH₃), 2.29 (s, 3H, CH₃), 3.78 (s, 3H, OCH₃), 4.59 (s, 1H, 3a-H), 6.99–7.85 (m, 8H, H arom). 13C{1H}NMR (CDCl₃; 75.47 MHz) δ: 19.20 (CH₂), 22.04 (CH₃), 55.60 (OCH₃), 59.36 (C-3a), 87.89 (C-5a), 118.01–159.65 (C arom.), 151.97 (C-3), 168.90 (C-4), 173.15 (C-6).

4.4.6. 3,5-di-(4-methoxyphenyl)-6a-methyl-3a,5,6,6a-tetrahydro-4H-pyrrolo[3,4-d]isoaxazole-4,6-dione 5he

Yield (0.347 g, 95%), white solid. M.p. = 198–200 °C. Anal. Calcd. For C₂₄H₂₄N₂O₅: C, 65.56; H, 4.96; N, 7.64%. Found: C, 65.40; H, 4.85; N, 7.70%. IR (KBr) υ ~ 1640 (C=O). 1H NMR (DMSO; 300 MHz) δ: 1.87 (s, 3H, CH₃), 3.83 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 4.54 (s, 1H, 3a-H), 6.93 (d, 2H) and 7.18 (d, 2H): AA'BB' part. J ~ 9 Hz, 7.05 (d, 2H) and 7.08 (d, 2H): AA'BB' part. J ~ 9 Hz. 13C{1H}NMR (DMSO; 75.47 MHz) δ: 19.61 (CH₃), 55.81 (OCH₃), 55.91 (OCH₃), 60.10 (C-3a), 87.91 (C-6a), 114.64–162.15 (C arom.), 152.60 (C-3), 170.27 (C-4), 173.57 (C-6).
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References


