SYNTHESIS OF 4, 6-DIARYL-4,6,7,8-TETRAHYDRO[1,4]OXAZEPINO[4,3-c]SYDNONE

Zhanbin Zhang* and Xinfang Duan

Department of Chemistry, Beijing Normal University, Beijing 100875, China
E-mail: zzbbnu@163.com

Abstract – Seven-membered ring fused sydnones, 4,6-diaryl-4,6,7,8-tetrahydro-[1,4]oxazepino[4,3-c]sydnones (2) were prepared via oxa-Pictet-Spengler reaction of 3-(3-phenyl-3-hydroxypropyl)sydnone (1) with aromatic aldehydes in the presence of Lewis acid. The reactions gave two stereoisomers (cis- and trans-), and the cis-isomers were the major products.

INTRODUCTION

Sydnones are a class of dipolar, mesoionic heteroaromatic compounds. Their unique physical properties, spectral properties and biological activities have attracted researcher’s attentions. Efficient syntheses of sydnone derivatives were also developed. These compounds can undergo a variety of reactions including electrophilic aromatic substitution (when unsubstituted at 4-position), 1,3-dipolar cycloaddition (with e.g. alkynes), acid induced cleavage to hydrazines (or products therefrom) and metallation at 4-position (when unsubstituted at 4-position) with subsequent electrophilic substitution. As a result they are useful building blocks for heterocycle’s preparations (e.g. pyrazole). In contrast to many reports on single-ring sydnone derivatives, fused-ring sydnones were relatively fewer. This paper reports the oxa-Pictet-Spengler reactions (Scheme 1) of sydnones (1), which provides an efficient synthetic approach to seven-membered ring fused sydnones, 4,6-diaryl-4,6,7,8-tetrahydro[1,4]oxazepino[4,3-c]sydnones (2).

![Scheme 1](image-url)
RESULTS AND DISCUSSION

In a typical oxa-Pictet-Spengler reaction, 2-arylethanol reacts with an aldehyde or ketone to give a
isochromane derivatives.⁶ Since sydnones are unstable to both acidic and basic media, we performed the
oxa-Pictet-Spengler reaction of 3-(3-phenyl-3-hydroxypropyl)sydnone (1) with aromatic aldehydes at
room temperature in dioxane or DME. Experiments found that BF₃-Et₂O was a mild and effective
catalyst while p-TsOH did not work under the same conditions. As listed in Table 1, eight
seven-membered ring fused sydnone derivatives were prepared successfully with total yield up to 86%. It
was also found that electron-rich aromatic aldehydes such as p-anisaldehyde and piperonal were unable to
react at the same reaction conditions.

Table 1. Synthesis of 4,6-diaryl-4,6,7,8-tetrahydro[1,4]oxazepino[4,3-c]sydnones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Product</th>
<th>Yield (%)</th>
<th>δ (H-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>cis-</td>
<td>trans-</td>
</tr>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>2a</td>
<td>52</td>
<td>21.4</td>
</tr>
<tr>
<td>2</td>
<td>4-BrC₆H₄</td>
<td>2b</td>
<td>46.5</td>
<td>20.5</td>
</tr>
<tr>
<td>3</td>
<td>3-BrC₆H₄</td>
<td>2c</td>
<td>54.2</td>
<td>10.4</td>
</tr>
<tr>
<td>4</td>
<td>2-O₂N₃C₆H₄</td>
<td>2d</td>
<td>45.2</td>
<td>0b</td>
</tr>
<tr>
<td>5</td>
<td>4-O₂N₃C₆H₄</td>
<td>2e</td>
<td>79</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>3-O₂N₃C₆H₄</td>
<td>2f</td>
<td>77.6</td>
<td>6.8</td>
</tr>
<tr>
<td>7</td>
<td>2,6-Cl₂C₆H₄</td>
<td>2g</td>
<td>67</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>2-ClC₆H₄</td>
<td>2h</td>
<td>56</td>
<td>0b</td>
</tr>
<tr>
<td>9</td>
<td>4-MeOC₆H₄</td>
<td>2i</td>
<td>0c</td>
<td>0</td>
</tr>
</tbody>
</table>

a Isolated yields, after silica gel column chromatography (eluent: petroleum ether-EtOAc).
b No trans-isomer was isolated.
c No cyclization product was observed at room temperature after 5 days.

High cis-selectivity for isochromans has been previously observed in the oxa-Pictet-Spengler reaction.⁷ In
our experiments, reactions of 1 with aromatic aldehydes are also stereoselective, giving the
cis-stereoisomer as major product. In the reactions of 1 with o-nitrobenzaldehyde and
o-chlorobenzaldehyde, only the cis-stereoisomers are isolated.

The definitive assignments of the cis-stereochemical relationship between the substituents at C-4 and C-6
was made by the nuclear NOE difference spectroscopy. For example, H-6 of cis-2f showed 6% signal
enhancement when H-4 was irradiated, while H-6 of trans-2f showed only 0.2% signal enhancement
when H-4 was irradiated, and H at the Ph group showed 1.2% signal enhancement. Since the chemical
shift of H-4 of cis-2 is smaller than that of trans-2, we can easily distinguish the cis- and trans-isomers by
the chemical shifts of H-4.
The solid state structure of cis-2g was determined by X-Ray diffraction (Figure 1), which shows that the cis-configuration of the substituents Ph and Ar in tetrahydro[1,4]oxazepine ring and the two substituents were at equatorial positions.

In summary, we have successfully established an efficient synthetic method for the preparation of tetrahydro[1,4]oxazepino[4,3-c]sydnones by the oxa-Pictet-Spengler cyclization. Manipulation of the sydnone ring is valuable in organic syntheses, and tetrhydro[1,4]oxazepino[4,3-c]sydnone is a useful precursor for the synthesis of fused pyrazole derivatives by the [3+2] cycloaddition with alkene or alkyne.

**EXPERIMENTAL**

Melting points were measured on a RY-1 apparatus and are uncorrected. Elemental analyses were carried out on an Elementar Vario El instrument. FT-IR spectra were measured on a Nicolet Avatar 360 spectrometer. $^1$HNMR (500MHz) spectra were recorded on Bruker Avance 500 NMR spectrometer with TMS as internal reference. Mass spectra (EI, 70eV) were taken on a Finigan GC2000/TRACE$^\text{TM}$MS mass spectrometer. Starting material (1) was prepared by literature produces.$^8$ All other chemicals were commercially available and were used as received.
General Procedure for the Reaction of 3-(3-Phenyl-3-hydroxypropyl)sydnone with Aromatic Aldehyde.

To a solution of compound (1) (440 mg, 2 mmol) in dioxane (15 mL) were added aromatic aldehyde (24 mmol) and boron trifluoride etherate (568 mg, 4 mmol) with stirring at rt. After the mixture was stirred at rt for 3 d, saturated aqueous NaHCO₃ solution (20 mL) was added, and the mixture was extracted with ethyl acetate (2×20 mL). The combined extracts were dried (Na₂SO₄) and the solvent was removed in vacuo. The crude mixture was separated by column chromatography over silica gel (petroleum ether/EtOAc=3:1) to yield trans-2 (minor) and cis-2 (major).

4,6,7,8-Tetrahydro-4,6-diphenyl[1,4]oxazepino[4,3-c]sydnone (cis-2a)
colorless crystals; mp 161-162°C (recrystallized from AcOEt/hexane); IR(KBr, cm⁻¹) ν 1746, 1491, 1199, 1091, 1062, 755, 698; ¹H NMR (CDCl₃) δ 7.28-7.53 (m, 10H, Ar-H), 5.83 (s, 1H), 4.95 (dd, J=9.9, 3.9 Hz, 1H), 4.82-4.87 (m, 1H), 4.63 (ddd, J=13.7, 6.9, 3.4 Hz, 1H), 2.55-2.62 (m, 1H), 2.32-2.40 (m, 1H); Anal. Calcd for C₁₈H₁₆N₂O₃: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.01; H, 5.50; N, 8.87. MS: 308 (M⁺), 309 (M⁺H⁺).

4,6,7,8-Tetrahydro-4,6-diphenyl[1,4]oxazepino[4,3-c]sydnone (trans-2a)
colorless crystals; mp 128-130°C (recrystallized from AcOEt/hexane); IR(KBr, cm⁻¹) ν 1732, 1512, 1492, 1453, 1186, 1065, 1004, 764, 744, 701; ¹H NMR (CDCl₃) δ 7.24-7.46 (m, 10H, Ar-H), 6.32 (s, 1H), 4.89 (d, J=9.5 Hz, 1H), 4.67 (m, 1H), 4.45 (t, J=12.9 Hz, 1H), 2.28 (m, 2H); Anal. Calcd for C₁₈H₁₆N₂O₃: C, 70.12; H, 5.45; N, 8.91. MS: 308(M⁺), 309(M⁺H⁺).

4-(4-Bromophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-c]sydnone (cis-2b)
colorless crystals; mp 176-178°C (recrystallized from AcOEt/hexane); IR(KBr, cm⁻¹) ν 1750, 1500 1080, 1020 780, 710; ¹H NMR(CDCl₃) δ 7.35-7.54 (m, 9H, Ar-H), 4.93 (dd, J=9.9, 3.3 Hz, 1H, CH-Ph), 5.74 (s, 1H, CH-Syd), 4.80, 4.60 (2m, 2H, CH₂-Syd), 2.55, 2.34 (2m, 2H, CH₂); Anal. Calcd for C₁₈H₁₅N₂O₃Br: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.42; H,3.98; N, 7.61. MS(FAB): 387(M⁺H⁺).
4.83 (ddd, $J=13.3, 8.6, 3.5$ Hz, 1H), 4.63 (ddd, $J=13.8, 7.2, 3.4$ Hz, 1H), 2.58 (m, 1H), 2.37 (m, 1H); Anal. Calcd for C$_{18}$H$_{15}$N$_2$O$_3$Br: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.67; H, 3.81; N, 7.35. MS: 387 (M+H)$^+$.  

4-(3-Bromophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-c]sydnone (trans-2c)  

colorless crystals; mp 112-113°C (recrystallized from AcOEt/hexane); IR(KBr, cm$^{-1}$)  $\nu$ 1750, 1500, 1180, 1080, 1020, 780, 760, 720; $^1$H NMR (CDCl$_3$) $\delta$ 7.17-7.55 (m, 9H, Ar-H), 6.20 (s, 1H, CH-Syd), 4.86 (m, 1H, CH-Ph), 4.42, 4.66 (2m, 2H, CH$_2$-Syd), 2.30 (m, 2H, CH$_2$); Anal. Calcd for C$_{18}$H$_{15}$N$_2$O$_3$Br: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.67; H, 3.81; N, 7.35. MS: 387 (M+H)$^+$.  

4,6,7,8-Tetrahydro-4-(2-nitrophenyl)-6-phenyl[1,4]oxazepino[4,3-c]sydnone (cis-2d)  
yellow crystals; mp 193-195°C (recrystallized from AcOEt/hexane); IR(cm$^{-1}$) $\nu$ 1734, 1525, 1345, 1072, 1057, 762, 732; $^1$H NMR(CDCl$_3$) $\delta$ 7.30-8.30 (m, 9H, Ar-H), 6.45 (s, 1H, CH-Syd), 5.04 (dd, $J=10.2, 1.8$ Hz, 1H), 4.80, 4.83 (2m, 2H, CH$_2$-Syd), 2.33, 2.51 (2m, 2H, CH$_2$); Anal. Calcd for C$_{18}$H$_{15}$N$_3$O$_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.32; H, 4.48; N, 11.62. MS: 354 (M+H)$^+$.  

4,6,7,8-Tetrahydro-4-(4-nitrophenyl)-6-phenyl[1,4]oxazepino[4,3-c]sydnone (cis-2e)  
yellow crystals; mp 182-183°C (recrystallized from AcOEt/hexane); IR(KBr, cm$^{-1}$) $\nu$ 1740, 1515, 1340, 1080, 1060, 1020, 850, 760, 740,700; $^1$H NMR(CDCl$_3$) $\delta$ 7.38-8.25 (m, 9H, Ar-H), 5.88 (s, 1H, CH-Syd), 4.98 (dd, $J=9.9, 2.7$ Hz, 1H, CH-Ph), 4.83, 4.69 (2m, 2H, CH$_2$-Syd), 2.53, 2.36 (2m, 2H, CH$_2$); Anal. Calcd for C$_{18}$H$_{15}$N$_3$O$_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.24; H, 4.17; N, 12.02.  

4,6,7,8-Tetrahydro-4-(3-nitrophenyl)-6-phenyl[1,4]oxazepino[4,3-c]sydnone (cis-2f)  
yellow crystals; mp 199-201°C (recrystallized from AcOEt/hexane); IR(KBr, cm$^{-1}$) $\nu$ 1740, 1515, 1350, 1080, 1020, 770, 705; $^1$H NMR (CDCl$_3$) $\delta$ 7.26-7.829 (m, 9H, Ar-H), 6.18 (s, 1H, CH-Syd), 4.88 (dd, $J=8.7, 3.6$ Hz, 1H, CH-Ph), 4.73, 4.45 (2m, 2H, CH$_2$-Syd), 2.39 (m, 2H, CH$_2$); Anal. Calcd for C$_{18}$H$_{15}$N$_3$O$_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.01; H, 4.20; N, 11.88. MS: 353(M$^+$), 354(M+H)$^+$.  

4,6,7,8-Tetrahydro-4-(3-nitrophenyl)-6-phenyl[1,4]oxazepino[4,3-c]sydnone (trans-2f)  
yellow crystals; mp 161-163°C (recrystallized from AcOEt/hexane); IR(KBr, cm$^{-1}$) $\nu$ 1760, 1545, 1360, 1080, 1030, 760, 720; $^1$H NMR (CDCl$_3$) $\delta$ 7.28-8.29 (m, 9H, Ar-H), 6.15 (s, 1H, CH-Syd), 4.91 (dd, $J=8.1, 4.5$ Hz, 1H, CH-Ph), 4.74, 4.49 (2m, 2H, CH$_2$-Syd), 2.45 (m, 2H, CH$_2$); Anal. Calcd for C$_{18}$H$_{15}$N$_3$O$_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.05; H, 4.20; N, 12.12. MS: 353(M$^+$), 354(M+H)$^+$.  

4-(2,6-Dichlorophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-c]sydnone (cis-2g)
colorless crystals; mp 201-203°C (recrystallized from AcOEt/hexane); IR(KBr, cm\(^{-1}\)) \(\nu\ 1740, 1500, 1440, 1100, 790, 770, 700\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\ 7.22-7.50\ (m, 8H, Ar-H), 6.48\ (s, 1H, CH-Syd), 5.11\ ((dd, \(J=7.3, 4.0\) Hz, 1H), 4.85 (ddd, 1H, \(J=14.1, 8.1, 1.8\) Hz), 4.60 (ddd, \(J=14.1, 9.2, 1.5\) Hz, 1H), 2.67, 2.45 (2m, 2H, CH\(_2\)); Anal. Calcd for C\(_{18}\)H\(_{14}\)N\(_2\)O\(_3\)Cl\(_2\): C, 57.31; H, 3.74; N, 7.43. Found: C, 57.51; H, 3.90; N, 7.17. MS: 376(M\(^+\)), 377(M+H\(^+\)).

4-(2,6-Dichlorophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-c]sydnone (trans-2g)

colorless crystals; mp 150-152°C (recrystallized from AcOEt/hexane); IR(KBr, cm\(^{-1}\)) \(\nu\ 1760, 1510, 1455, 1220, 1120, 1080, 805, 790, 720\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\ 7.25-7.50\ (m, 8H, Ar-H), 6.60\ (s, 1H, CH-Syd), 5.30\ (m, 1H, CH-Ph), 5.04, 4.90 (2m, 2H, CH\(_2\)-Syd), 2.72-2.39 (2m, 2H, CH\(_2\)); Anal. Calcd for C\(_{18}\)H\(_{14}\)N\(_2\)O\(_3\)Cl\(_2\): C, 57.31; H, 3.74; N, 7.43. Found: C, 57.10; H, 3.65; N, 6.85. MS: 377(M+H\(^+\)).

4-(2-Chlorophenyl)-4,6,7,8-tetrahydro-6-phenyl[1,4]oxazepino[4,3-c]sydnone (cis-2h)

colorless crystals; mp 197-199°C (recrystallized from AcOEt/hexane); IR(KBr, cm\(^{-1}\)) \(\nu\ 1749, 1492, 1209, 1199, 1046, 1017, 760, 698\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\ 7.25-7.50\ (m, 9H, Ar-H), 6.01\ (s, 1H, CH-Syd), 5.03 (dd, \(J=10.2, 2.1\) Hz, 1H), 4.79 (m, 2H), 2.48 (m, 1H), 2.32 (m, 1H); Anal. Calcd for C\(_{18}\)H\(_{15}\)N\(_2\)O\(_3\)Cl: C, 63.39; H, 4.73; N, 8.19. Found: C, 63.07; H, 4.41; N, 8.17. MS: 343(M+H\(^+\)).

X-Ray Structural Analysis of cis-2g

Molecular formula C\(_{18}\)H\(_{14}\)N\(_2\)O\(_3\)Cl\(_2\), formula weight 377.21, crystal description colorless prism, crystal size 0.40 x 0.40 x 0.20 mm, monoclinic, space group P2(1)/n, \(a=12.397(2)\)\(\AA\), \(b=11.032(2)\)\(\AA\), \(c=14.528(3)\)\(\AA\), \(\alpha=90°\), \(\beta=100.44(2)°\), \(\gamma=90°\), \(V=1954.0(6)\) \(\AA^3\), \(Z=4\), \(\lambda(\text{MoK} \alpha)=0.71073\) \(\AA\), \(D_c=1.282\text{Mg/cm}^3\), \(\mu=0.350\text{mm}^{-1}\), F(000)=776, collected 1.99°< \(\theta\) < 27.99°, Limiting indices, \(-1<=h<=16, -1<=k<=14, -19<=l<=19\), Goodness-of-fit on F\(^2\) 0.929, Final R indices \([I>2\sigma(I)]\) \(R_1=0.0839, wR_2=0.2638\), R indices (all data) \(R_1=0.1435, wR_2=0.2973\).

REFERENCES