New and efficient synthesis of 1,4-oxazines through the reaction of acetylenic esters and nitrosonaphthols in the presence of phosphine derivatives

Razieh Mohebat,*a Afshin Yazdani Elah Abadi,b Aliakbar Soltani,a and Mitra Saghafi*a

aDepartment of Chemistry, Islamic Azad University, Yazd Branch, P.O. Box 89195-155, Yazd, Iran
bYoung Researchers and Elite Club, Yazd Branch, Islamic Azad University, Yazd, Iran
P.O. Box 89195-155, Yazd, Iran
E-mail: mohebat@iauyazd.ac.ir

DOI: http://dx.doi.org/10.3998/ark.5550190.p009.543

Abstract
Protonation of the reactive 1:1 intermediate produced in the reaction between phosphine derivatives and dialkyl acetylenedicarboxylates with 1-nitroso-2-naphthol or 2-nitroso-1-naphthol leads to a vinylphosphonium salt which undergoes intramolecular Wittig reaction to produce 1,4-oxazine derivatives without any catalyst in good yields.

Keywords: Nitrosonaphthols, acetylenic esters, phosphine derivatives, 1,4-oxazines, intramolecular Wittig reaction

Introduction
Synthesis of compounds containing nitrogen and oxygen in a ring is of growing importance by virtue of their presence in numerous biologically important compounds.1-4 Therefore, the development of the design and synthesis of new diverse polycyclic heterocycles with potential medicinal and biological activity from readily available starting materials in a cost and time effective manner has received significant attention in research on organic, combinatorial, and medicinal chemistry.5-11

Oxazines and their derivatives are heterocyclic compounds containing one nitrogen and one oxygen.12 Oxazine heterocycles have special interest because they constitute an important class of natural and non natural products and show useful biological activities.13 The 1,4-oxazine scaffold is a structural subunit of many naturally occurring and synthetic bioactive compounds and have diverse biological activities such as antiulcer,14 antihypertensive,15 antifungal,16 anticancer17 and anti-thrombotic compound.18
In recent years, the Wittig reaction\textsuperscript{19-21} has received much attention in organic synthesis because of its high reliability and its importance for the construction of carbon-carbon bonds.\textsuperscript{22}

Furthermore, the intramolecular Wittig reaction\textsuperscript{23-25} is one of the most powerful methods for cycloalkene and unsaturated heterocyclic compounds synthesis. While the intramolecular Wittig reaction has attracted significant attention for the syntheses of highly functionalized natural products, the intramolecular Wittig reaction between dialkyl acetylenedicarboxylates and phosphine derivatives in the presence of nitroso compounds has not been reported. In this area, the first time in 1976, McKillop and Sayer established the synthesis of naphthoxazines from dimethyl acetylenedicarboxylate and nitrosonaphthol copper complexes.\textsuperscript{26}

Schonberg and Brosowski\textsuperscript{27} have extended the Wittig reaction by the use of nitrosobenzene instead of a carbonyl compound (Figure 1) and our attempts to effect a similar reaction between phosphine derivatives 1 and dialkyl acetylenedicarboxylates 2 with nitrosonaphthols 3, 4 to give 1,4-oxazines 5, 6, were successful and proved to be an excellent method for the construction of C=N double bonds (Scheme 1).

![Figure 1. Wittig reaction by the use of nitrosobenzene instead of a carbonyl compound.](image)

Considering the importance of oxazines and in continuation of our research on the development of new synthetic methods in heterocyclic chemistry,\textsuperscript{28-33} herein we wish to describe the preparation of functionalized 1,4-oxazine derivatives via intramolecular Wittig reaction in good yields (Scheme 1, Table 1).

![Scheme 1. Synthesis of functionalized 1,4-oxazine derivatives.](image)
Table 1. Synthesis of functionalized 1,4-oxazine derivatives in the presence of nitrosonaphthols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Nitrosonaphthol</th>
<th>Product</th>
<th>Yield$^{b,d}$ (%)</th>
<th>Yield$^{c,d}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td><img src="image" alt="5a" /></td>
<td>5a</td>
<td>85</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td><img src="image" alt="5b" /></td>
<td>5b</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>t-Bu</td>
<td><img src="image" alt="5c" /></td>
<td>5c</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td><img src="image" alt="6a" /></td>
<td>6a</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td><img src="image" alt="6b" /></td>
<td>6b</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td><img src="image" alt="6c" /></td>
<td>6c</td>
<td>80</td>
<td>75</td>
</tr>
</tbody>
</table>

a All reactions were carried out following the general procedure outlined in the experimental section. b The reaction was carried out in the presence of triphenylphosphine. c The reaction was carried out in the presence of tri-m-tolylphosphine. d Isolated yields.

Results and Discussion

1,4-Oxazine derivatives can be synthesized through a one-pot condensation reaction between phosphine derivatives with electron deficient acetylenic esters in the presence of nitrosonaphthols in toluene under reflux conditions. The reaction of triphenylphosphine 1a or tri-m-tolylphosphine 1b and dialkyl acetylenedicarboxylates 2 with 1-nitroso-2-naphthol 3 or 2-nitroso-1-naphthol 4 proceeded spontaneously in toluene, and was complete within a few hours. The results are summarized in Table 1. As it is clear from Table 1, the reactions were efficiently promoted in the presence of triphenylphosphine leading to increased yields compared to tri-m-tolylphosphine.

The $^1$H and $^{13}$C NMR spectra of the crude products clearly indicated the formation of dialkyl 3H-naphtho[2,1-b][1,4]oxazine-2,3-dicarboxylates 5. No other product could be detected by NMR spectroscopy. The compounds 5a-c were separated from triarylphosphine oxide, and their structures were deduced from their elemental analyses and infrared (IR) and $^1$H NMR and $^{13}$C
NMR spectroscopic data. The mass spectra of these compounds displayed molecular ion peaks at m/z 299, 327, and 383, respectively, which is consistent with the formation of a 1:1:1 adduct of phosphine derivatives, dialkyl acetylenedicarboxylate, and 1-nitroso-2-naphthol. The $^1$H NMR spectrum of 5a exhibited two single sharp lines at $\delta$ 3.96 and 3.99 ppm, characteristic for the two methyl protons of the esters; the CH proton resonates at $\delta$ 6.23 ppm. The other aromatic protons resonate as four doublets and two triplets at the range $\delta$ 7.20–7.92 ppm. The $^{13}$C NMR spectrum of 5a showed sixteen distinct resonances in agreement with the proposed structure (see Experimental section). The $^1$H and $^{13}$C NMR spectra of 5b–c are similar to that of 5a, except for the signals of the ester group. The structural assignments made on the basis of the NMR spectra of compound 5a were supported by its IR spectrum. The CH of aliphatic, carbonyl and C=N groups exhibited strong absorption bands at 2920, 1755, 1723 and 1646 cm$^{-1}$.

Also, the reaction of triphenylphosphine or tri(m-tolyl)phosphine 1 and dialkyl acetylenedicarboxylates 2 in the presence of 2-nitroso-1-naphthol 4 led to 6 in good yields (Scheme 1). The results are given in Table 1.

Structures of compounds 6a–c were assigned by IR, $^1$H NMR, $^{13}$C NMR and mass spectral data. The $^1$H and $^{13}$C NMR spectra of 6a–c are similar to that of 5a–c and partial assignments of these resonances are given in the Experimental. For example, the NMR spectrum of 6a exhibited 13 proton resonances and 16 carbon resonances in agreement with the proposed structure.

A plausible mechanism for the formation of compound 5 is illustrated in Scheme 2. On the basis of the well-established chemistry of trivalent phosphorus nucleophiles, it is reasonable to assume that compound 7 results from the initial addition of triphenylphosphine or tri-m-tolylphosphine 1 to the acetylene diester 2 and the subsequent protonation of the 1:1 adduct by the 1-nitroso-2-naphthol 3. Then, the positively charged ion intermediate 8 is attacked by the conjugate anion of 1-nitroso-2-naphthol 9 to form the ylide 10 and cyclization of this zwitterionic intermediate produces the oxaphosphorane 11, which undergoes an intramolecular Wittig reaction to produce triphenylphosphine oxide and the product 5 (Scheme 2).
Conclusions

We have described an effective and novel intramolecular Wittig reaction for the preparation of 1,4-oxazine derivatives from nitrosonaphthols and acetylenic esters in the presence of triphenylphosphine or tri(m-tolyl)phosphine. The present procedure offers the advantage of carrying out the reaction under mild and neutral conditions. The starting materials and reagents can be mixed without any activation or modification which provides an efficient and economical method for the synthesis of 1,4-oxazines in good yields. Therefore, this procedure described here provides an acceptable one-pot method for the construction of C=N double bonds.

Experimental Section

General. All melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on Bruker DRX-400 Avance spectrometer at solution in CDCl$_3$. 

Scheme 2. Suggested mechanism for formation of 1,4-oxazine derivatives.
using TMS as internal standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Synthesis of 1,4-oxazine derivatives (5,6). To a magnetically stirred solution of triphenylphosphine or tri(m-tolyl)phosphine (1 mmol) and 1-nitroso-2-naphthol or 2-nitroso-1-naphthol (1 mmol) in toluene (10 mL) was added dropwise a mixture of dialkyl acetylenedicarboxylate (1 mmol) in toluene (2 mL) at ambient temperature over 10 min. The reaction mixture was allowed to stir at room temperature for 1 h and then reflux for 3–5 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure and the residual solid was purified by column chromatography (Merck silica gel 60, 230–400 Mesh ASTM) using n-hexane/EtOAc 3:1 as eluent. The solvent was removed under reduced pressure and the product was obtained.

Dimethyl 3H-naphtho[2,1-b][1,4]oxazine-2,3-dicarboxylate (5a). Yellow crystals; yield in the presence of Ph₃P: 0.254 g (85%), in the presence of (m-MeC₆H₄)₃P: 0.242 g (81%); mp 220-222 °C; IR (KBr) (v max cm⁻¹): 2920 (CH of aliphatic), 1755, 1723 (2C=O), 1646 (C=N); ¹H NMR (400 MHz, CDCl₃): δ 3.96, 3.99 (6H, s, 2OCH₃), 6.23 (1H, s, CH), 7.19 (1H, d, J 8.8 Hz, Ar-H), 7.47 (1H, t, J 8.0 Hz, Ar-H), 7.53 (1H, d, J 8.4 Hz, Ar-H), 7.64 (1H, t, J 8.0 Hz, Ar-H), 7.81 (1H, d, J 8.4 Hz, Ar-H), 7.89 (1H, d, J 8.8 Hz, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 52.1, 53.4 (2OCH₃), 84.1 (CH), 112.6, 120.0, 122.3, 123.9, 126.2, 127.0, 127.5, 127.6, 129.6, 130.8, 137.6 (C-Ar), 150.6 (C=N), 160.1, 165.5, 168.3 (2C=O) ppm; MS (m/z, %): 299 (M⁺, 7); Anal. Calcd. for C₁₆H₁₃NO₅: C, 64.21; H, 4.38; N, 4.68 %. Found: C, 64.38; H, 4.46; N, 4.51%.

Diethyl 3H-naphtho[2,1-b][1,4]oxazine-2,3-dicarboxylate (5b). Yellow crystals; yield in the presence of Ph₃P: 0.268 g (82%), in the presence of (m-MeC₆H₄)₃P: 0.262 g (80%); mp 236-238 °C; IR (KBr) (v max cm⁻¹): 2917 (CH of aliphatic), 1746, 1720 (2C=O), 1642 (C=N); ¹H NMR (400 MHz, CDCl₃): δ 1.20, 1.25 (6H, t, J 7.2 Hz, 2CH₃), 4.18, 4.28 (4H, q, J 7.2 Hz, 2OCH₂), 6.30 (1H, s, CH), 7.20 (1H, d, J 8.8 Hz, Ar-H), 7.46 (1H, t, J 8.0 Hz, Ar-H), 7.57 (1H, d, J 8.4 Hz, Ar-H), 7.68 (1H, t, J 8.4 Hz, Ar-H), 7.79 (1H, d, J 8.0 Hz, Ar-H), 7.92 (1H, d, J 8.8 Hz, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 14.7, 15.6 (2CH₃), 60.1, 61.5 (2OCH₂), 86.3 (CH), 113.5, 121.1, 123.0, 125.2, 126.7, 128.9, 130.6, 131.9, 138.8 (C-Ar), 153.4 (C=N), 166.4, 170.6 (2C=O) ppm; MS (m/z, %): 327 (M⁺, 12); Anal. Calcd. for C₁₈H₁₇NO₅: C, 66.05; H, 5.23; N, 4.28%. Found: C, 66.21; H, 5.40; N, 4.12%.

Di-tert-butyl 3H-naphtho[2,1-b][1,4]oxazine-2,3-dicarboxylate (5c). Yellow crystals; yield in the presence of Ph₃P: 0.299 g (78%), in the presence of (m-MeC₆H₄)₃P: 0.276 g (80%); mp 241-243 °C; IR (KBr) (v max cm⁻¹): 2932 (CH of aliphatic), 1744, 1728 (2C=O), 1648 (C=N); ¹H NMR (400 MHz, CDCl₃): δ 1.31, 1.42 (18H, s, 2C(CH₃)₃), 6.32 (1H, s, CH), 7.21 (1H, d, J 8.4 Hz, Ar-H), 7.45 (1H, t, J 8.0 Hz, Ar-H), 7.55 (1H, d, J 8.4 Hz, Ar-H), 7.67 (1H, t, J 8.0 Hz, Ar-H), 7.80 (1H, d, J 8.4 Hz, Ar-H), 7.93 (1H, d, J 8.4 Hz, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 27.6, 28.2 (2OC(CH₃)₃), 80.2, 82.6 (2OC(CH₃)₃), 85.3 (CH), 112.8, 119.7, 120.1, 121.2, 126.6, 126.7, 129.7, 131.2, 133.2, 147.6 (C-Ar), 150.2 (C=N), 166.7, 168.6 (2C=O) ppm; MS (m/z, %): 383
General Papers

Arkivoc 2016 (iv) 1-9

© ARKAT-USA, Inc.

Page 7

(M+, 10); Anal. Calcd. for C_{22}H_{25}NO_{5}: C, 68.91; H, 6.57; N, 3.65 %. Found: C, 69.04; H, 6.46; N, 3.78%.

Dimethyl 2H-naphth[1,2-b][1,4]oxazine-2,3-dicarboxylate (6a). Yellow crystals; yield in the presence of Ph3P: 0.260 g (87%), in the presence of (m-MeC₆H₄)₃P: 0.251 g (84%); mp 225-227 °C; IR (KBr) (νmax cm⁻¹): 2918 (CH of aliphatic), 1745, 1716 (2C=O), 1638 (C=N); ¹H NMR (400 MHz, CDCl₃): δ 3.87, 3.91 (6H, s, 2OCH₃), 6.28 (1H, s, CH), 7.57 (1H, d, J 8.4 Hz, Ar-H), 7.66 (1H, d, J 8.4 Hz, Ar-H), 7.89 (1H, t, J 8.0 Hz, Ar-H), 7.94 (1H, d, J 8.4 Hz, Ar-H), 8.03 (1H, t, J 8.0 Hz, Ar-H), 8.21 (1H, d, J 8.4 Hz, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 52.0, 54.1 (2OCH₃), 84.3 (CH), 112.2, 121.5, 122.8, 124.1, 127.5, 127.9, 128.3, 129.8, 131.6, 137.8 (C-Ar), 153.1 (C=N), 167.5, 170.4 (2C=O) ppm; MS (m/z, %): 299 (M⁺, 10).

Anal. Calcd. for C_{16}H_{13}NO_{5}: C, 64.21; H, 4.38; N, 4.68 %. Found: C, 64.11; H, 4.50; N, 4.54%.

Diethyl 2H-naphth[1,2-b][1,4]oxazine-2,3-dicarboxylate (6b). Yellow crystals; yield in the presence of Ph₃P: 0.268 g (82%), in the presence of (m-MeC₆H₄)₃P: 0.268 g (82%); mp 231-233 °C; IR (KBr) (νmax cm⁻¹): 2920 (CH of aliphatic), 1744, 1713 (2C=O), 1640 (C=N); ¹H NMR (400 MHz, CDCl₃): δ 1.22, 1.26 (6H, t, J 7.2 Hz, 2CH₃), 4.14, 4.22 (4H, q, J 7.2 Hz, 2OCH₂), 6.25 (1H, s, CH), 7.42 (1H, d, J 8.8 Hz, Ar-H), 7.50 (1H, d, J 8.4 Hz, Ar-H), 7.81 (1H, t, J 8.0 Hz, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 14.3, 15.7 (2CH₃), 60.3, 62.7 (2OCH₂), 84.2 (CH), 112.7, 121.8, 123.5, 124.8, 126.3, 127.1, 128.4, 129.9, 132.7, 136.8 (C-Ar), 156.2 (C=N), 169.1, 172.5 (2C=O) ppm; MS (m/z, %): 327 (M⁺, 12).

Anal. Calcd. for C_{18}H_{17}NO_{5}: C, 66.05; H, 5.23; N, 4.28 %. Found: C, 65.92; H, 5.11; N, 4.40 %.

Di-tert-butyl 2H-naphth[1,2-b][1,4]oxazine-2,3-dicarboxylate (6c). Yellow crystals; yield in the presence of Ph₃P: 0.306 g (80%), in the presence of (m-MeC₆H₄)₃P: 0.287 g (75%); mp 238-240 °C; IR (KBr) (νmax cm⁻¹): 2937 (CH of aliphatic), 1744, 1710 (2C=O), 1635 (C=N); ¹H NMR (400 MHz, CDCl₃): δ 1.37, 1.46 (18H, s, 2C(CH₃)₃), 6.39 (1H, s, CH), 7.41 (1H, d, J 8.4 Hz, Ar-H), 7.54 (1H, d, J 8.0 Hz, Ar-H), 7.83 (1H, t, J 8.0 Hz, Ar-H), 7.88 (1H, d, J 8.4 Hz, Ar-H), 8.01 (1H, t, J 8.0 Hz, Ar-H), 8.13 (1H, d, J 8.4 Hz, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 27.5, 29.0 (2OC(CH₃)₃), 81.1, 82.8 (2OC(CH₃)₃), 85.8 (CH), 111.9, 117.1, 121.3, 123.2, 126.5, 127.0, 131.1, 132.5, 133.8, 148.6 (C-Ar), 153.2 (C=N), 165.7, 169.3 (2C=O); MS (m/z, %): 383 (M⁺, 8).

Anal. Calcd. for C_{22}H_{25}NO_{5}: C, 68.91; H, 6.57; N, 3.65 %. Found: C, 68.80; H, 6.69; N, 3.48%.

Acknowledgments

We gratefully acknowledge financial support from the Research Council of the Islamic Azad University of Yazd.
References

   http://dx.doi.org/10.1039/np8603000001
   http://dx.doi.org/10.1021/cr00021a011
   http://dx.doi.org/10.1039/np9613000075
   http://dx.doi.org/10.1126/science.287.5460.1964
   http://dx.doi.org/10.1016/S1367-5931(00)00096-X
   http://dx.doi.org/10.1002/anie.199502591
   http://dx.doi.org/10.1021/cr950027e
   http://dx.doi.org/10.1126/science.1962206
    http://dx.doi.org/10.1039/c1gc16129f
    http://dx.doi.org/10.1039/c2gc16388h
    http://dx.doi.org/10.3390/12030345
    http://dx.doi.org/10.1248/cpb.39.2937
    http://dx.doi.org/10.1248/cpb.39.2896
    http://dx.doi.org/10.1016/S0968-0896(02)00038-X
    http://dx.doi.org/10.1021/jm00362a015
    http://dx.doi.org/10.1016/S0960-894X(98)00386-2
    http://dx.doi.org/10.1021/cr00094a007
   http://dx.doi.org/10.1002/9780470147306.ch1
   http://dx.doi.org/10.1002/jlac.199719970704
   http://dx.doi.org/10.1055/s-1974-23432
   http://dx.doi.org/10.1016/0040-4020(80)80068-8
25. Heron, M. Heterocycles 1995, 41, 2357.
   http://dx.doi.org/10.3987/REV-95-474
   http://dx.doi.org/10.1021/jo00868a039
   http://dx.doi.org/10.1002/cber.19590921033
   http://dx.doi.org/10.1016/174751914X13921421504937
   http://dx.doi.org/10.1016/174751914X13921460686140
   http://dx.doi.org/10.1016/174751912X1346509708885
   http://dx.doi.org/10.1080/00397911.2011.627105
   http://dx.doi.org/10.1080/00397910902778027
   http://dx.doi.org/10.1016/030823410X12710015235147
   http://dx.doi.org/10.1021/cr00029a003
   http://dx.doi.org/10.1016/S0040-4029(01)81950-X