

## 5(4*H*)-Oxazolones. Part XIII. A New Synthesis of 4-Ylidene-5(4*H*)-oxazolones by the Stille Reaction.

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**Abstract** 4-Chloromethylene-2-phenyl-5(4*H*)-oxazolone **1** was used as the starting material for the preparation of a series of 4-ylideneoxazolones **3** by the Stille reaction. When compound **1** was reacted with organostannanes **2** in the presence of the palladium catalyst, oxazolones **3** were obtained in good yields in mild reaction conditions. © 1998 Published by Elsevier Science Ltd. All rights reserved.

**Keywords:** Oxazolones; Tin and compounds; Coupling reaction; Stille reaction; Stereochemistry

### INTRODUCTION

The use of 5(4*H*)-oxazolones as starting materials for the preparation of other heterocycles or for the synthesis of modified  $\alpha$ -amino acids or their derivatives is proved by many papers since more than a century<sup>1</sup> but their use is still explored.<sup>2</sup> In recent years our attention<sup>3</sup> was focused on the use of 4-chloromethylene-2-phenyl-5(4*H*)-oxazolone **1** as starting material because the presence of the chlorine atom allows reaction with both nucleophilic heteroatoms and carbanions, through an addition-elimination mechanism, resulting in the preparation of different classes of oxazolones or new rings when a second nucleophilic centre is present which can react with the carbonyl group. Despite its numerous synthetic uses,<sup>2</sup> to our knowledge, the possibility of reacting oxazolone **1** with organometallic reagents has not been considered. It is known that the Stille reaction<sup>4</sup> is a good method for the construction of carbon-carbon bonds because of the mild reaction conditions, the availability of different organostannanes and their compatibility with different functional groups, in our case with the lactone group. Furthermore, acyl chlorides react with organostannane reagents giving the corresponding ketones,<sup>5</sup> and oxazolone **1** is vinillogous to an acyl chloride. Accordingly, the possibility of using the oxazolone **1** as starting material to synthesize different 4-ylidene-5(4*H*)-oxazolones through cross-coupling with stannane reagents was evaluated. Our approach offers an alternative to the classical Erlenmeyer method<sup>1a</sup> and other preparations<sup>2</sup> of 4-ylidene-5(4*H*)-oxazolones. In some cases it is the sole way to obtain the title compounds, because of the unavailability of the required starting carbonyl compound or the possibility of its degradation in the usual reaction

conditions. Our method allows the preparation of functionalized oxazolones **3** in good yields and with controlled stereochemistry at the double bond.

## RESULTS

The chlorooxazolone **1** was found to be an excellent substrate for Stille-based functionalization and underwent efficient palladium-catalysed coupling with a range of stannanes. The possibility using different stannanes in order to introduce vinyl, alkynyl, aryl, heteroaryl and alkyl groups has been considered and several palladium catalysts and reaction conditions have been tried. To find the best reaction conditions, oxazolone **1** was reacted with tri(*n*-butyl)vinylstannane **2a** using tetrakis(triphenylphosphine)palladium [(PPh<sub>3</sub>)<sub>4</sub>Pd], or dichlorobis(triphenylphosphine)palladium [(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>Pd], or benzylchlorobis(triphenylphosphine)palladium [PhCH<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub>Cl] as catalysts and in chloroform or HMPA as solvents.

Good results were obtained by using chloroform as solvent at reflux and [PhCH<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub>Cl] (1%) as catalyst. The reaction was complete in 15 min and the 4-allylidene-2-phenyl-5(4*H*)-oxazolone **3a** was isolated in 50% yield (Scheme 1). Using the same reaction conditions, but operating at room temperature, the stannane **2a** did not react with oxazolone **1**; however, the use of HMPA as the solvent, both at 25 and 65 °C, instead resulted in a mixture of compounds in which oxazolone **3a** was detectable in traces. The other two catalysts were not efficient for the coupling reaction confirming the efficiency of the benzylchloro bis(triphenylphosphine)palladium in the condensation between stannanes and chloro derivatives having an acyl chloride like reactivity.<sup>5</sup> As observed, the best reaction conditions appeared to be chloroform as solvent at reflux and [PhCH<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub>Cl] (1%) as catalyst and they were used for all subsequent reactions. Good yields (98-80%) and short reaction times were observed when oxazolone **1** was reacted with stannanes **2b-e** giving the corresponding oxazolones **3b-e** functionalized at the methylene carbon with phenyl, *p*-methoxyphenyl, 2-furyl and 2-thienyl groups, respectively (Scheme 1).

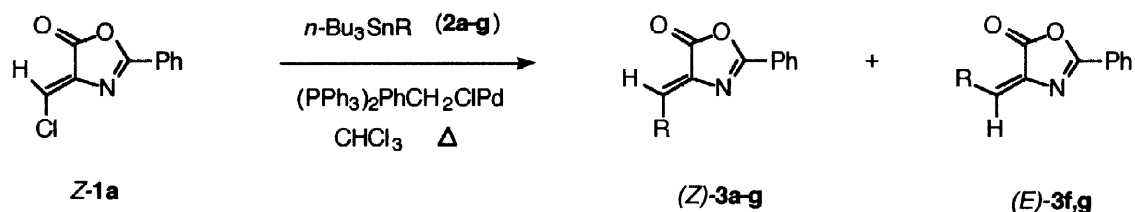
In the cases described above, the stereochemistry of the double bond is the same as in the starting oxazolone **1**, for which a *Z*-configuration was demonstrated,<sup>3c</sup> and it was confirmed by comparison with analytical and spectroscopic data described in the literature for compounds **3b-e**. The structure of the new oxazolone **3a** was given on the basis of its IR, <sup>1</sup>H- and <sup>13</sup>C-NMR spectra and the *Z*-configuration of the double bond was assigned by analogy with the above results. This is in agreement with the literature<sup>4a</sup> in which it is reported that the stereochemistry of the starting halovinyl compound is usually preserved in the Stille reaction.

The possibility to link an alkynyl group to the methylene carbon has been considered. The use of tri(*n*-butyl)ethynylstannane gave unsatisfactory results because of the formation of a complex mixture of degradation products. Instead, the tri(*n*-butyl)-2-phenylethynylstannane **2f** reacted with **1** giving the oxazolone **3f** as a mixture of *Z*- and *E*-isomers (22:1 ratio). The reaction proceeded very quickly (15 min) and in good yield (60 %) (Scheme 1).

The Stille reaction of **1** with allyltri(*n*-butyl)stannane was unsuccessful. However with tetramethylstannane **2g** the oxazolone **3g** was obtained (75%) as a mixture of two isomers (*Z/E*, 16:1). In this case the reaction was conducted in a sealed tube and a longer reaction time was needed (6 h) (Scheme 1).

The stereochemistry of oxazolones **3f,g** was assigned from the chemical shift of the vinyl proton, which in the *E*-isomer is at lower field than in the *Z*-isomers<sup>6a,b</sup> and this assignment was confirmed from the literature<sup>6c</sup> for the known isomeric compounds **3g**.

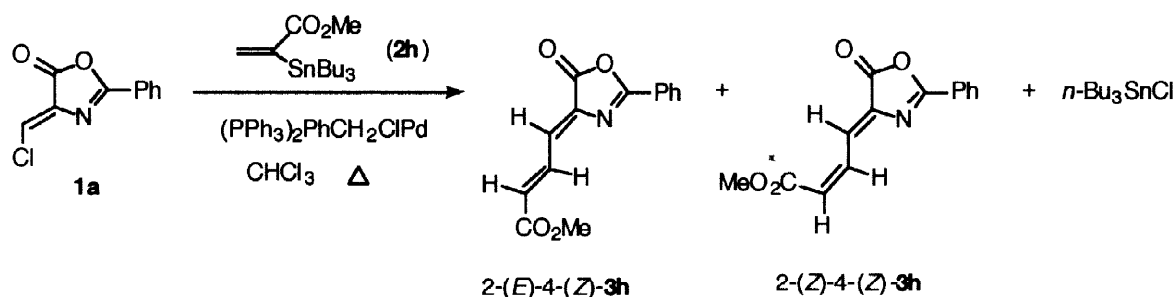
Scheme 1



**2a; 3a** R = CH<sub>2</sub>=CH  
**2b; 3b** R = Ph  
**2c; 3c** R = *p*-MeOC<sub>6</sub>H<sub>4</sub>  
**2d; 3d** R = 2-furyl  
**2e; 3e** R = 2-thienyl  
**2f; 3f** R = PhC≡C  
**2g; 3g** R = Me

Finally, the tri(*n*-butyl)-1-methoxycarbonylvinylstannane **2h** was reacted with oxazolone **1**. It appeared to be less reactive than the other tin reagents (reaction time 15 h; yield 36 %) and a mixture of two isomeric oxazolones **3h** (2 : 1) was isolated (Scheme 2).

Scheme 2



As shown, the outcome of the reaction is different, involving the cross-coupling between the side chain carbon of **1** and C-3 of the tin reagent. This result is not unprecedented as the same behaviour was observed when stannane **2h** was reacted with iodobenzene.<sup>7</sup> The proposed mechanism in this case is an Heck reaction followed by a protodestannylation. An attempt to change the addition by operating in presence of CuI resulted in a mixture of tarry products.

In conclusion, starting from readily available reagents as oxazolone **1** and organostannanes **2**, a practical and efficient synthesis of 4-ylideneoxazolones has been described. It has to be noted that the classical Erlenmeyer synthesis of oxazolone derivatives often affords a mixture containing *Z/E* isomers in similar amounts (*e.g.* for **3g**: *Z/E*, 3 : 1),<sup>6c</sup> while our synthesis gave oxazolones **3** with high stereocontrol at the double bond.

## EXPERIMENTAL

Melting points were determined using a Büchi 510 (capillary) and Electrothermal apparatus. IR spectra were recorded on a JASCO IR Report 100 spectrophotometer. NMR spectra were obtained with Bruker AC 200 and Varian Gemini 200 instruments. TLC was performed on ready-to-use silica gel plates, and column chromatography on silica gel [Kieselgel 60-70 230 ASTM (Merck)] with the eluent indicated.

**Materials.** Compound **1**<sup>8,9</sup> and organostannanes **2c**<sup>10</sup> and **2h**<sup>11</sup> were prepared according to known procedures. The catalyst and tin reagents **2a, b, e-g** were purchased from Aldrich. Anhydrous ethanol-free CHCl<sub>3</sub> was used.

**General Procedure for Stille Reaction.** A solution of oxazolone **1** (207 mg, 1 mmol), stannane **2** (1.1 mmol) and PhCH<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub>Cl (8 mg, 0.01 mmol) in CHCl<sub>3</sub> (10 ml) was stirred at reflux under nitrogen for the time indicated in Table 1. After solvent evaporation, the crude reaction mixture was chromatographed on silica gel (pentane/CH<sub>2</sub>Cl<sub>2</sub>, 1:0 to 0:1) giving, after recrystallization, pure oxazolone **3**.

**(Z)-4-Allylidene-2-phenyl-5(4H)-oxazolone (3a):** Calcd. for C<sub>12</sub>H<sub>9</sub>NO<sub>2</sub> (199.21): C 72.35, H 4.55, N 7.03 %; Found: C 72.00, H 4.40, N 6.88 %; IR (nujol) cm<sup>-1</sup>: 1790 (CO), 1640 (CN); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.20-7.40 (m, 5 H, H<sub>aryl</sub>), 7.27 (ddd, J<sub>1,2</sub> = 11.4, J<sub>cis</sub> = 9.9, J<sub>trans</sub> = 16.9 Hz, 1 H, H<sub>allyl-2</sub>), 6.96 (d, J<sub>1,2</sub> = 11.4 Hz, 1 H, H<sub>allyl-1</sub>), 5.87 (d, J<sub>trans</sub> = 16.9 Hz, 1 H, H<sub>allyl-3</sub>), 5.78 (d, J<sub>cis</sub> = 9.9 Hz, 1 H, H<sub>allyl-3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 167.1 (CO), 163.3 (C-2), 135.4 (C-4), 133.7, 132.8, 132.1, 129.4, 128.7 (CH<sub>aryl</sub> and CH<sub>allyl</sub>), 129.2, 126.0 (CH<sub>2</sub> and C<sub>aryl</sub>).

**2-Phenyl-4-(3-phenylprop-2-ynylidene)-5(4H)-oxazolone (3f): (Z)-3f:** Calcd. for C<sub>18</sub>H<sub>11</sub>NO<sub>2</sub> (273.28): C 79.10, H 4.06, N 5.13 %; Found: C 79.00, H 4.28, N 5.00 %; IR (nujol) cm<sup>-1</sup>: 2180 (C=C), 1780 (CO), 1620 (CN); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.22-8.17, 7.68-7.38 (m, 10 H, H<sub>aryl</sub>), 6.67 (s, 1 H, CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 166.2, 165.1 (CO and C-2), 142.6 (C-4), 134.3-128.8 (CH<sub>aryl</sub>), 125.5, 122.6 (C<sub>aryl</sub>), 112.9 (CH), 108.7, 86.6 (C=C). **(E)-3f:** <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.15-8.08, 7.70-7.38 (m, 10 H, H<sub>aryl</sub>), 6.78 (s, 1H, CH).

Table 1.

Compd.	Reaction Time (h)	Yield (%)	m.p. (°C) (Solvent)	Lit. (°C)	Compd.	Reaction Time (h)	Yield (%)	m.p. (°C)	Lit. (°C)
<b>3a</b>	0.15	50	111 (A) <sup>a</sup>	-	<b>3e</b>	1	82	180 (C) <sup>a</sup>	177 <sup>14</sup>
<b>3b</b>	0.30	98	165 (B) <sup>a</sup>	166 <sup>12</sup>	<b>3f</b>	0.15	60 <sup>b</sup>	120 (B) <sup>a,c,d</sup>	-
<b>3c</b>	6	80	159 (C) <sup>a</sup>	159 <sup>13</sup>	<b>3g</b>	6	75 <sup>b</sup>	97 (E) <sup>a,c</sup>	98 <sup>15</sup>
<b>3d</b>	1	97	171 (C) <sup>a</sup>	171 <sup>12</sup>	<b>3h</b>	15	40 <sup>b</sup>	190 (D) <sup>a,e</sup>	-

<sup>a</sup> A: pentane/Et<sub>2</sub>O; B: Et<sub>2</sub>O; C: *i*-Pr<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>; D: Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>; E: pentane/CH<sub>2</sub>Cl<sub>2</sub>.

<sup>b</sup> Mixture of two diastereoisomers

<sup>c</sup> (Z)-isomer

<sup>d</sup> The *E*-isomer of **3f** is described.<sup>16</sup>

<sup>e</sup> 2-(*E*),4-(*Z*)-isomer

**Methyl 4-(5-oxo-2-phenyloxazol-4-ylidene)but-2-enoate (3h).** Calcd. for C<sub>14</sub>H<sub>11</sub>NO<sub>4</sub> (257.25): C 65.37, H 4.31, N 5.44 %; Found: C 65.10, H 4.43, N 5.20 %; 2-(*E*),4-(*Z*)-**3h**: IR (nujol) cm<sup>-1</sup>: 1780 (CO), 1710 (CO<sub>2</sub>Me), 1640 (CN); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.20-7.50 (m, 5 H, H<sub>aryl</sub>), 8.08, 6.97, 6.38 (dd, d, d, AMX system  $J_{3-4} = 11.3$ ,  $J_{2-3} = 16.4$  Hz, 3 H, H-3, H-4, H-2), 3.84 (s, 3 H, OMe); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 166.6, 166.2, 165.2 (CO, C-2), 140.0 (C-4), 137.6, 134.5, 130.1, 129.5, 129.2, 129.1 (CH<sub>aryl</sub> and CH<sub>allyl</sub>), 125.5 (C<sub>aryl</sub>), 53.0 (Me). 2-(*Z*),4-(*Z*)-**3h**: IR (nujol) cm<sup>-1</sup>: 1780 (CO), 1705 (CO<sub>2</sub>Me), 1640 (CN); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.20-7.10 (m, 2 H, H<sub>aryl</sub>), 7.68-7.49 (m, 5 H, H-3 and H-4), 6.17 (d,  $J = 11.3$  Hz, 1 H, H-2), 3.82 (s, 3 H, OMe); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 166.4, 166.3, 165.0 (CO, C-2), 140.1 (C-4), 136.5, 134.3, 129.5, 129.1, 126.2, 126.0 (CH<sub>aryl</sub> and CH<sub>allyl</sub>), 125.7 (C<sub>aryl</sub>), 52.2 (Me).

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- Reference 8 describes the synthesis of **1** to which the *E*-configuration was assigned. The Authors reported that the photoisomerization of *E*-**1** resulted in a mixture of *E*- and *Z*-oxazolones to which signals of methylene protons at  $\delta = 7.25$  and  $\delta = 5.30$  (CDCl<sub>3</sub>) were assigned, respectively. Instead, we assigned the *Z*-configuration to the synthesized product on the following grounds. The photoisomerization of **1** produced a mixture of isomers with signals at  $\delta = 7.21$  and  $\delta = 7.20$  (CD<sub>2</sub>Cl<sub>2</sub>) which were associated to *E*- and *Z*-isomers, respectively. Two facts support our conclusion: it is known<sup>6</sup> that *Z*-oxazolones are the more stable and are photoisomerized to the less stable *E*-isomers; for all *Z/E* couples the chemical shifts of the methylene protons are in the range of  $\delta = 6.8$ -8.0 and the signals for compound *E* appears at lower field.
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