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Reactivity of bis-vinylphosphates obtained from imide derivatives. Synthesis of 2,6-disubstituted 1,4-dihydropyridines

Deborah Mousset, Isabelle Gillaizeau,* Jwanro Hassan, Franck Lepifre, Pascal Bouyssou and Gérard Coudert*

Institut de Chimie Organique et Analytique, UMR 6005, Université d'Orléans, BP 6759, 45067 Orléans cedex 2, France

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Abstract—The Pd-catalyzed functionalization of lactam-derived vinyl phosphates has become an important tool in the last decade for the synthesis of nitrogen-containing heterocycles. By using this method, we were able to introduce alkenyl, aryl and heteroaryl groups on bis-vinylphosphate derivatives to provide efficient access to 2,6-disubstituted 1,4-dihydropyridines.

Due to the rich chemistry of nitrogen-containing compounds and their evident biological interest, synthesizing N-heterocycles has been a central and important theme within organic chemistry. The functionalization of lactams by Pd-catalyzed coupling reactions of the corresponding vinyl phosphates has gained increasing importance in the synthesis of heterocyclic compounds. In fact, phosphate-activated intermediates were found to be more robust than the corresponding triflates. Nicolaou et al. especially reported on the phosphate activation of both N-acyllactam[1] and lactone[2] derivatives. The usefulness of lactam-derived vinyl phosphates was also described by Occhiato and co-workers.[3] Recently, N-alkyl ketene aminal phosphates derived from N-alkyl lactam precursors were applied to asymmetric syntheses[4] and also to an intramolecular Heck cyclization.[5]

In a previous work, we reported the preparation of cyclic six-, seven- and thirteen-membered ene-carbamates substituted on C2 by aryl or heteroaryl groups using an extension of the Suzuki reaction involving the palladium coupling of boronic acids and lactam-derived vinyl phosphates.[6] Encouraged by the success of this model reaction, extension of this approach for the preparation of bis-substituted dihydropyridine derivatives was envisaged. In fact dihydropyridines (DHPs) show interesting features that make them very attractive for use in organic synthesis. Furthermore few examples of 2,6-disubstituted dihydropyridines have been described and most of them have been synthesized from the corresponding pyridine or pyridinium salt.[7] We wish to report herein an efficient preparation of 2,6-disubstituted dihydropyridines using the Pd-catalyzed coupling reactions of the bis-vinylphosphates **3** and **4** according to a methodology previously developed in our group.[8]

As shown in Scheme 1, both *N*-Boc glutarimide derivatives **1** and **2** were prepared in high yield (respectively, in 84% and 95% yield) by reaction of the corresponding glutarimide with di-*tert*-butyldicarbonate in acetonitrile for 15 h. Treatment of both imides **1** and **2** with LDA at −78 °C in THF provided a hardly soluble bis-enolate, which was trapped by reaction with diphenylchlorophosphate (2.4 equiv, THF, −78 to 20 °C) to give, as expected after complete conversion, bis-vinylphosphates **3** and **4**. These compounds were then isolated by silica gel column chromatography, respectively, in 64% and 70% yields as stable compounds.

These new bis-vinylphosphates **3** and **4** were then subjected to typical organometallic coupling reactions. Firstly, according to a Stille-type coupling, the reaction of bis-vinylphosphate **3** in the presence of catalytic $Pd(PPh_3)_4$ and anhydrous LiCl in refluxing THF for 2 h remarkably afforded the desired compounds **5**, **6** and **7** in fair to good yields (cf. Scheme 2). The results of these coupling reactions are presented in Table 1.

Keywords: 2,6-Disubstituted 1,4-dihydropyridines; Ene-carbamate; Vinylphosphate; Palladium coupling reaction.
* Corresponding authors. Tel.: +33 238 494 583; fax: +33 238 417 281; e-mail addresses: isabelle.gillaizeau@univ-orleans.fr; gerard.coudert@univ-orleans.fr

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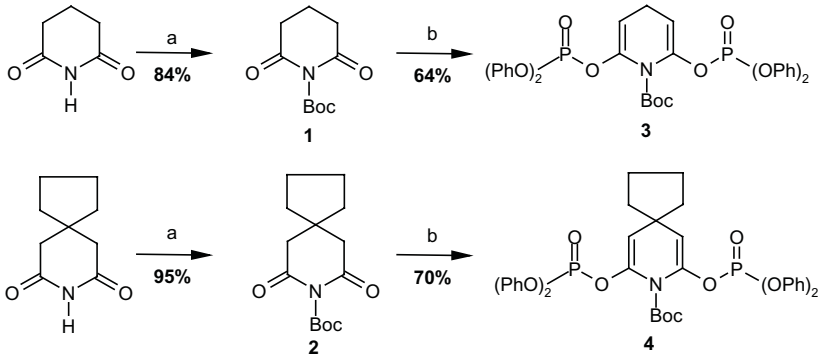
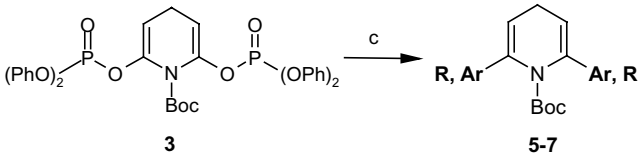
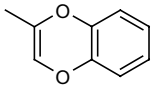
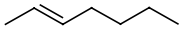


Scheme 1. Reagents and conditions: (a) Boc_2O, DMAP cat., CH_3CN, RT, 15 h; (b) (i) 2.6 equiv LDA, THF, −78 °C, 2 h; (ii) 2.4 equiv $ClP(O)(OPh)_2$, −78 °C to RT, 15 h.



Scheme 2. Reagents and conditions: (c) 10 mol% $Pd(PPh_3)_4$, 4 equiv $RSnBu_3$ or $ArSnBu_3$, 3 equiv LiCl, THF, 3 h, reflux (cf. Table 1).

Table 1. Stille coupling reactions on bis-vinylphosphate **3**[a]

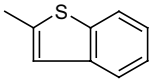
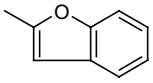
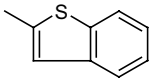
Bis-vinylphosphate	R or Ar	Products	Yield (%)
3		**5**	**88**
3		**6**	**66**
3		**7**	**54**

[a] All the compounds were fully characterized by analytical and spectroscopic methods.

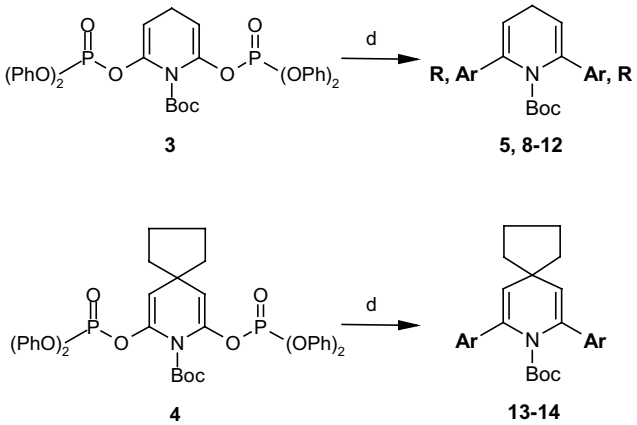
One of the attractive features of our approach lies in its inherent versatility since a wide range of reactants could be used. A Pd-catalyzed Suzuki–Miyaura coupling reaction[9] of the bis-vinylphosphates **3** and **4** was subsequently applied. Using different boronic acid derivatives the corresponding 2,6-disubstituted dihydropyridines **5**, **8**–**14** were easily isolated in good yields (cf. Table 2 and Scheme 3). In the case of bis-phenyl derivative **8**, the coupling reaction was complete in only 30 min. For the introduction of the unsubstituted vinyl moiety (compound **5**, Tables 1 and 2), a better yield was observed with the Stille coupling compared to the Suzuki–Miyaura reaction (88% yield instead of 54% yield). The Heck reaction had already been reported as a serious competitor in the case of vinylboronic esters.[10]

In conclusion, we have described the syntheses of 2,6-dialkenyl-, 2,6-diaryl- and 2,6-diheteroaryl-1,4-dihydropyridines through a series of palladium-catalyzed reactions via the corresponding bis-vinylphosphates. All these compounds are of great interest as intermediates in the elaboration of more complex molecules exhibiting biological activity. Further studies on the

Table 2. Suzuki coupling reactions on bis-vinylphosphates **3** and **4**[a]

Bis-vinylphosphate	R or Ar	Products	Yield (%)
3		**8**[b]	**88**
3		**9**	**83**
3		**10**	**25**
3		**11**	**60**
3		**12**	**61**
3		**5**	**54**
4		**13**	**85**
4		**14**	**70**

[a] All the compounds were fully characterized by analytical and spectroscopic methods.
[b] Reaction time 30 min.



Scheme 3. Reagents and conditions: (d) (i) 10 mol% $PdCl_2(PPh_3)_2$ THF, RT, 10 min; (ii) 3 equiv $ArB(OH)_2$ or $RB(OH)_2$, 2 equiv Na_2CO_3 2 M, EtOH, reflux, 3 h (cf. Table 2).

reactivity of these 1,4-dihydropyridine derivatives are currently in progress in our laboratory.

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8. Typical procedure: Preparation of the bis-vinylphosphate (**3**): To a solution of 1-(*tert*-butoxycarbonyl)-2,6-dioxopiperidine **1** (4.69 mmol, 1.0 g) in THF (9 mL) at −78 °C under argon, LDA (12.19 mmol, 2 M in hexane, 6.1 mL) was added dropwise. After stirring for 2 h at −78 °C, diphenyl chlorophosphate (11.25 mmol, 2.4 mL) was added and the mixture was allowed to warm up to room temperature over 15 h. The reaction was quenched by slow addition of H_2O. Ethyl acetate was then added, the organic layer was separated and dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by flash column chromatography (silica gel, petroleum ether/EtOAc 6:4) to afford compound **3** (2.03 g, 64%) as a brown oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.41 (s, 9H, *t*-Bu); 2.75–2.78 (m, 2H, H_4); 5.36–5.40 (m, 2H, H_3 et H_5); 7.14–7.33 (m, 20H, H_{ar}). ^{13}C NMR (62.8 MHz; $CDCl_3$) δ (ppm) 21.5 (C_4); 27.9 (C(CH_3)$_3$); 83.9 (C(CH$_3$)$_3$); 101.7 (C_3, C_5); 120.2, 120.3, 125.6, 129.9 (C_{ar}); 141.4, 141.5 (C_6, C_2); 150.4, 150.6 (C_{ar}); 151.3 (C=O). IR ν_{max} (NaCl film) 3071, 2980 and 2934 (C–H); 1743 (C=O); 1590, 1493 and 1457 (C=C); 1345 (P=O). SM (IS) *m/z* 678,50 $[M + H]^+$.
   General procedure for the Stille coupling reaction. Preparation of 1-(*tert*-butoxycarbonyl)-2,6-divinyl-1,4-dihydropyridine (**5**). To a stirred solution of bis-vinyl phosphate **3** (0.74 mmol, 500 mg) in THF (2.5 mL), tributyl(vinyl)tin (2.95 mmol, 863 μL), anhydrous lithium chloride (4.43 mmol, 188 mg) and $Pd(PPh_3)_4$ (0.074 mmol, 51 mg), were added under argon. The mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was diluted with water, ethyl acetate was then added. The organic layer was separated, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/EtOAc 8:2). Compound **5** was isolated as an orange solid. Yield: 151 mg (88%). Mp 134–135 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.44 (s, 9H, *t*-Bu); 2.74 (t, 2H, H_4, J = 5 Hz); 5.08 (d, 2H, $H_{2'}$ and $H_{2''}$, J_{cis} = 10 Hz); 5.35 (d, 2H, $H_{2'}$ and $H_{2''}$, J_{trans} = 17 Hz); 5.70 (t, 2H, H_3 and H_5, J = 5 Hz); 6.35(dd, 2H, $H_{1'}$ and $H_{1''}$, J_{cis} = 10 Hz and J_{trans} = 17 Hz). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ (ppm) 24.6 (C_4); 28.2 (C(CH_3)$_3$); 81.4 (C(CH$_3$)$_3$); 112.8 (CH_2=); 119.3 (C_3, C_5); 133.1 (CH=); 141.8 (C_2, C_6); 152.8 (C=O). IR ν_{max} (KBr) 2979, 2930 (C–H); 1715 (C=O); 1596. SM (IS) *m/z* 234 $[M + H]^+$.
   General procedure for the Suzuki coupling reaction. Preparation of 1-(*tert*-butoxycarbonyl)-2,6-diphenyl-1,4-dihydropyridine (**8**). To a solution of bis-vinyl phosphate **3** (0.74 mmol, 500 mg) in THF (2.5 mL) under argon $PdCl_2(PPh_3)_2$ (0.074 mmol, 51 mg) was added. The mixture was stirred during 15 min then phenylboronic acid (3.69 mmol, 449 mg), 2 M Na_2CO_3 (aq) (1.25 mL) and a few drops of EtOH were added. The mixture was refluxed for 30 min. After cooling, ethyl acetate was added, the organic layer was separated and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by flash column chromatography (silica gel, petroleum ether/EtOAc 8:2). Compound **8** was isolated as a white solid. Yield: 305 mg (88%). Mp 126–127 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.03 (s, 9H, *t*-Bu); 2.94 (t, 2H, H_4, J = 5 Hz); 5.78 (t, 2H, H_3 and H_5, J = 5 Hz); 7.24–7.40 (m, 6H, H_{ar}); 7.52–7.57 (m, 4H, H_{ar}). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ (ppm) 24.9 (C_4); 27.6 (C(CH_3)$_3$); 81.3 (C(CH$_3$)$_3$); 116.9 (C_3, C_5); 125.4, 127.3, 128.3, 138.9 (C_{ar}); 142.6 (C_2, C_6); 152.3 (C=O). IR ν_{max} (KBr) 2971, 2930, 2812 (C–H); 1716 (C=O); 1670, 1629, 1598. HRMS (IE) *m/z* calcd for $[C_{22}H_{23}NO_2-{\cdot}CO_2$-*t*-Bu$]^+$ 232.1126; found 232.1112.
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