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Stereospecific formation of enynephosphonates via palladium-catalyzed cross-coupling reaction of β-organotelluro vinylphosphonates with alkynes

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Abstract—β-Organotelluro vinylphosphonates **1** undergo direct coupling reaction with terminal alkynes in the presence of $PdCl_2$/CuI in methanol at room temperature to give enynephosphonates **3** with retention of configuration in good yields.

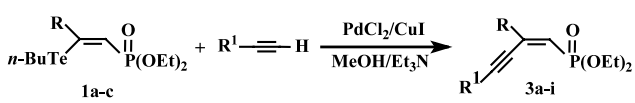
Recently, the discovery of strong antifungal[1] agents and new powerful antitumor antibiotics[2] has stimulated intense interest in the chemistry of enynes,[3] which is at the origin of the biological properties of these substances. Thus, one would anticipate that phosphonate-containing enynes would also be useful as building blocks for this purpose,[4,5] since a number of useful functional group transformations can be achieved by the introduction and sequential manipulation of phosphonates.[6]

However, so far, only one method of preparation of these compounds has been disclosed, by palladium-mediated cross-coupling reaction of α-iodo-vinylphosphonates with 1-alkynes.[7]

On the other hand, vinylic tellurides are important synthetic intermediates because of their easy transformation to other organic compounds with retention of configuration.[8] Due to our interest in new synthetic applications of these compounds,[9] we decided to study the coupling reaction of β-organotelluro vinylphosphonates **1** with 1-alkynes, which could give rise to the potentially very useful enynephosphonates **3** (Scheme 1).

Initially, we started our investigations using the cross-coupling of β-organotelluro vinylphosphonate **1b** with 1-alkynes. This reaction was very sensitive to the nature of the catalysts. The role of palladium(0) and palladium(II) was evidenced with 1-heptyne in methanol and triethylamine as base. When this reaction was carried out in the presence of different catalysts, such as $Pd(OAc)_2$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2$ and CuI, the cross-coupling was not observed. However, when $PdCl_2$ was used with copper salt (CuI) the reaction proceeded with high yield. The nature of the amine was also very important. The best results were obtained with triethylamine (83%). Diethylamine and diisopropylamine furnished the product in lower yields (60 and 50%, respectively). With pyridine, pyrrolidine or piperydine, no enynephosphonate was formed. We also investigated the influence of the solvent in this cross-coupling reaction. THF, dichloromentane, and benzene did not give the expected enynephosphonate. In acetonitrile, *N*,*N*-dimethylformamide, a small amount of cross-coupling product was observed. However, the use of methanol afforded enynephosphonates in high yields.

Thus, the optimum condition for the coupling, as described in Scheme 1, was found to be the use of $PdCl_2$/CuI (20 mol% each), methanol (10 mL), β-organotelluro vinylphosphonates **1** (1 mmol), the appropriate



1a - R = Ph; 1b - R = *n*-Bu; 1c - R = H

Scheme 1.

Keywords: cross-coupling; enynes; palladium; tellurium; phosphonate; telluride.

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1-alkyne (2 mmol) and Et_3N (1 mmol) at room temperature.[10] Using this methodology, we prepared several enynephosphonates **3a–j** in good yields (Table 1). The formation of products **3** was confirmed by NMR spectral analysis. The stereoisomeric purities of **3a–j** were equal to those of starting β-organotelluro vinylphosphonates **1**, due to the complete retention of configuration in this type of reaction.[11] The stereochemistry of the di-substituted vinylic phosphonate **3j** was easily established. We observed a double doublet at 6.40 ppm with coupling constants of $J_{cis\text{-}H,H}=13$ Hz and $J_{trans\text{-}H,P}=48$ Hz, typical of *cis* positioned protons (signal due to the olefinic proton β to phosphorus). The proton α resonates at 5.98 ppm as a double doublet with coupling constants of $J_{cis\text{-}H,H}=13$ Hz and $J_{gem\text{-}H,P}=17$ Hz.

The required starting β-organotelluro vinylphosphonates **1** can be prepared in good yields by highly stereoselective addition of sodium organyl chalcogenolates to alkynylphosphonates, as recently described by us[12] and later by others.[13]

In summary, we have developed the Pd(II)/CuI-catalyzed cross-coupling reaction of the β-organotelluro vinylphosphonates with 1-alkynes and established a new stereoselective route to β-alkynylvinylphosphonates (enynephosphonates) in good yields. The reaction proceeds cleanly under mild conditions, and tolerates many sensitive functional groups, like alcohols and phosphonates.

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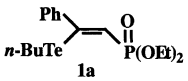
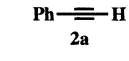
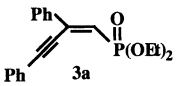
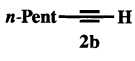
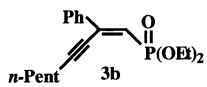
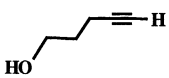
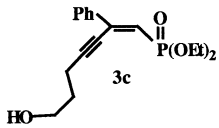
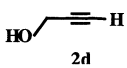
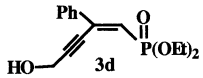
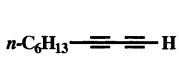
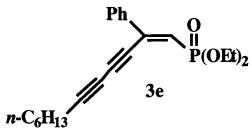
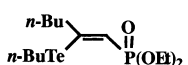
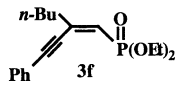
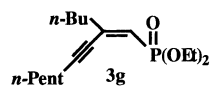
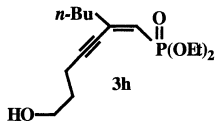
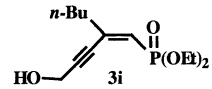
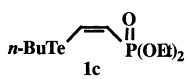
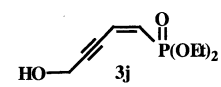
Table 1. Synthesis of enynephosphonates **3** according to Scheme 1

Entry	β-Organotelluro vinylphosphonates **1**	Alkyne **2**	Product **3**	Reaction Time / h	Product **3**[a] Yield %
1	 **1a**	 **2a**	 **3a**	8	73
2	**1a**	 **2b**	 **3b**	6	75
3	**1a**	 **2c**	 **3c**	5	80
4	**1a**	 **2d**	 **3d**	5	84
5	**1a**	 **2e**	 **3e**	8	85
6	 **1b**	**2a**	 **3f**	7	75
7	**1b**	**2b**	 **3g**	6	83
8	**1b**	**2c**	 **3h**	6	80
9	**1b**	**2d**	 **3i**	5	82
10	 **1c**	**2d**	 **3j**	4	75

[a] Isolated yield.

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10. **Pd(II)-catalyzed cross-coupling reaction of β-organotelluro vinylphosphonates 1 with alkynes: general procedure**: To a solution of $PdCl_2$ (20 mol%, 0.035 g), CuI (20 mol%, 0.038 g) in MeOH (10 mL) and Et_3N (1 mmol) at 25°C under an argon atmosphere, were added β-organotelluro vinylphosphonates **1** (1 mmol) and the appropriate alkyne (2 mmol). The mixture was stirred at room temperature for the time indicated in Table 1, treated with a NH_4Cl saturated solution (5 mL), and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash silica gel chromatography eluting with hexane/ethyl acetate (1:1) to give the product enynephosphonates **3**. **Selected spectral and analytical data for 3b**. ^1H NMR (200 MHz, $CDCl_3$): $\delta=$ 7.73–7.51 (m, 2H), 7.40–7.14 (m, 3H), 6.28 (d, 1H, $J_{P-H}=14.98$ Hz), 4.25–4.01 (m, 4H), 2.45 (t, 2H, $J=6.54$ Hz), 1.71–1.11 (m, 6H), 1.31 (t, 6H, $J_{P-H}=6.96$ Hz), 0.86 (t, 3H, $J=6.96$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta=$ 140.87 (d, $^3J_{P-C}=2.8$ Hz), 138.1 (d, $^2J_{P-C}=20.45$ Hz), 130.12, 128.82, 127.18, 119.61 (d, $^1J_{P-C}=191.4$ Hz), 103.36, 78.06 (d, $^3J_{P-C}=8$ Hz), 62.23 (d, $^2J_{P-C}=5.55$ Hz), 31.55, 28.41, 22.54, 20.28, 16.80 (d, $^3J_{P-C}=6.5$ Hz), 14.30; IR (KBr, film; cm^{-1}) 2980; 2904; 2870; 2229; 1585; 1561; 1445; 1391; 1334; 1236; 1162; 1028; 970; 837; 759; 691. LRMS (rel. int.) m/z 334 (65), 278 (83), 222 (95), 195 (81), 141 (100) 115 (55) 103 (19), 91 (24), 77 (27), 29 (76).
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