ORGANIC LETTERS

2000
Vol. 2, No. 24
3873−3875

# A New One-Pot Synthesis of Alkynylphosphonates

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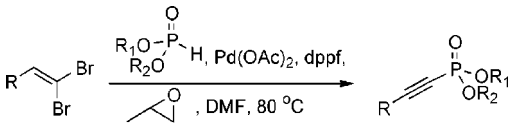
**Received September 19, 2000**

## ABSTRACT




**A method for the palladium-catalyzed synthesis of alkynylphosphonates from 1,1-dibromo-1-alkenes has been developed. In general, the best catalyst system for this transformation was found to be $Pd(OAc)_2$, dppf, *H*-phosphonate, propylene oxide, DMF, 80 °C. The reaction appears tolerant of a range of functional groups in both the 1,1-dibromo-1-alkene and *H*-phosphonate coupling partners. The synthesis of a backbone-modified thymidine dimer is used to illustrate the application of this methodology in the synthesis of complex target molecules.**

Recent work has shown that 1,1-dibromo-1-alkenes are useful electrophiles in palladium-catalyzed cross-coupling reactions. The ability of a palladium(0) catalyst to undergo stereoselective oxidative insertion into the *trans*-carbon−bromine bond has led to a new method for the stereoselective synthesis of a range of substituted olefins.[1] During the course of their work studying the stereoselective Stille coupling reactions of 1,1-dibromo-1-alkenes, Zapata[2] et. al., and more recently Shen[3] et. al., observed that under certain conditions the major products of this reaction were substituted enynes rather than the expected bromodienes. In an extension to this work, Shen[4] et. al. have shown that 1,1-dibromo-1-alkenes can also be used as precursors to diynes in a process related to the Sonagashira coupling.

As part of a project examining the use of transition metal-catalyzed carbon−phosphorus cross-coupling reactions in synthesis, we noticed a similar reactivity of 1,1-dibromo-1-alkenes to that reported by Zapata and Shen and have used this to develop a one-pot synthesis of substituted alkynylphosphonates. This methodology provides a convenient route to a range of alkynylphosphonates, which themselves may be used as precursors to a range of other useful functionality such as $\beta$-ketophosphonates,[5] vinylogous phosphonamides[6] and 2,2-disubstituted vinylphosphonates.[7] Our interest in this transformation arose from a chance discovery made during work examining the synthesis of backbone-modified nucleic acids via a palladium-catalyzed coupling of vinyl bromides and *H*-phosphonates.[8] While attempting to synthesize the bromovinylphosphonate **2** via a stereoselective palladium-catalyzed monocoupling between dibromide **1** and dimethyl phosphite,[9] we found that the major product was in fact the alkynylphosphonate **3** (63%) (Scheme 1).[10]

To explore the generality of this transformation, we synthesized a range of 1,1-dibromo-1-alkenes (see Table 1)

(1) (a) Shen, W. *Synlett* **2000**, 737. (b) Xu, C.; Negishi, E. *Tetrahedron Lett.* **1999**, *40*, 431. (c) Shen, W.; Wang, L. *Tetrahedron Lett.* **1998**, *39*, 7625. (d) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912. (e) Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russell, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551. (f) Minato, A. *J. Org. Chem.* **1991**, *56*, 4052. (g) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509. (h) Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 6759. (i) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965.

(2) Zapata, A. J.; Ruiz, J. *J. Organomet. Chem.* **1994**, *479*, C6.

(3) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873.

(4) Shen, W.; Thomas, S. A. *Org. Lett.* **2000**, *2*, 2857.

(5) (a) Poss, A. J.; Belter, R. K. *J. Org. Chem.* **1987**, *52*, 4810. (b) Chattha, M. S.; Aguiar, A. M. *J. Org. Chem.* **1973**, *38*, 2908. For use in synthesis, see: Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 6429.

(6) Chattha, M. S.; Aguiar, A. M. *J. Org. Chem.* **1973**, *38*, 820.

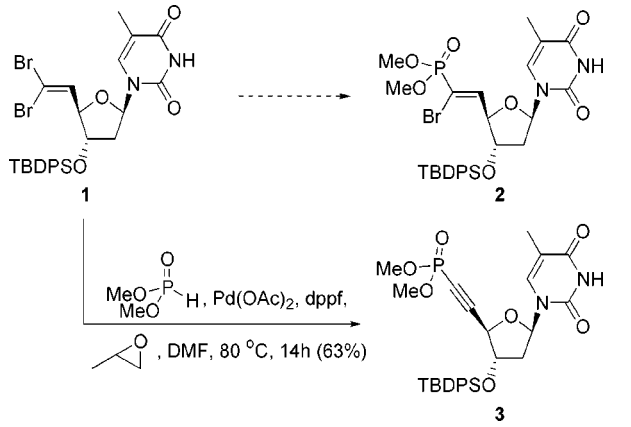
(7) Gil, J. M.; Oh, D. Y. *J. Org. Chem.* **1999**, *64*, 2950.

(8) (a) Abbas, S.; Hayes, C. J. *Tetrahedron Lett.* **2000**, *41*, 4513. (b) Abbas, S.; Hayes, C. J., *Synlett* **1999**, 1124.

(9) For an example of a Nickel-catalyzed monocoupling, see: Kazankova, M. A.; Trostyanskaya, I. G.; Lutsenko, S. V.; Beletskaya, I. P. *Tetrahedron Lett.* **1999**, *40*, 569.

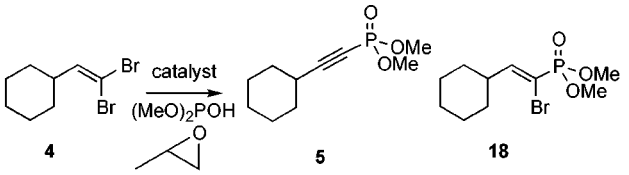
10.1021/ol0066173 CCC: $19.00 
**Published on Web 11/10/2000**

**Scheme 1**




using standard methodology[11] and studied their cross-coupling reactions. The first substrate to be examined was the cyclohexyl-substituted 1,1-dibromo-1-alkene **4** (Scheme 2). We were pleased to find that under conditions identical

**Scheme 2**



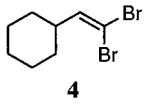
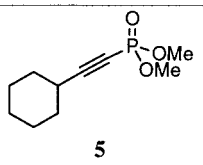
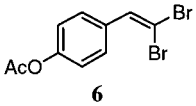
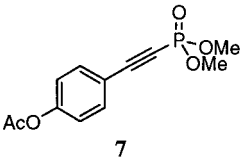
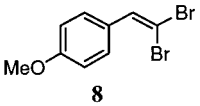
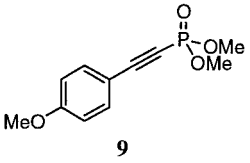
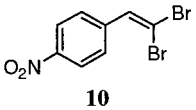
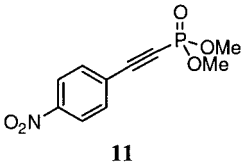
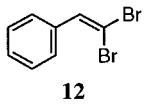
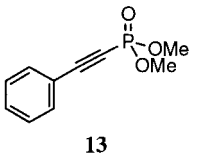
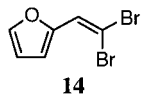
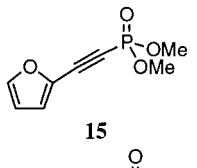
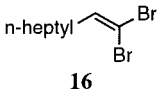
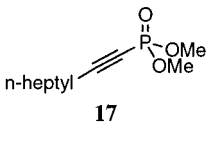

| solvent[a] | catalyst | yield of **5** (%) | yield of **18** (%) |
|---|---|---|---|
| DMF | $Pd(OAc)_2$, dppf | 76 | 0 |
| DMF | $Pd_2(dba)_3$, dppf | 43 | trace |
| THF | $Pd(OAc)_2$, dppf | 41 | 24 |
| toluene | $Pd(OAc)_2$, dppf | 48 | 15 |

[a] All reactions were heated using an oil bath at 80 °C.

to those used for the formation of **3** from **1** (i.e., $Pd(OAc)_2$ (0.2 equiv), dppf[12] (0.4 equiv), dimethyl phosphite (2.0 equiv), propylene oxide (3.0 equiv), DMF, 80 °C, 14 h), **4** was cleanly converted into the corresponding alkynylphosphonate **5** in 76% yield. Because of its partial water solubility and subsequent difficulties with extraction, the isolated yield of the desired product **5** was substantially reduced if we performed an aqueous workup at the end of the reaction. We found that the product was best isolated by removing the solvent in vacuo followed by silica gel chromatography of the resulting residue.

In an attempt to eliminate the need to remove DMF in vacuo, we examined the coupling reaction in lower-boiling

**Table 1.** Preparation of Alkynylphosphonates

| starting material | product[a] | yield[b] (%) |
|---|---|---|
|  **4** |  **5** | 76 (35) |
|  **6** |  **7** | 68 |
|  **8** |  **9** | 73 |
|  **10** |  **11** | 27 (31) |
|  **12** |  **13** | 63 |
|  **14** |  **15** | 16 (60) |
|  **16** |  **17** | 66 (27) |

[a] Reaction conditions: $Pd(OAc)_2$ (0.2 equiv), dppf (0.4 equiv), *H*-phosphonate (2.0 equiv), propylene oxide (3.0 equiv), DMF, 80 °C, 14 h. [b] The yields in parentheses were obtained when dppf was replaced with TFP as ligand; all other conditions were identical.

solvents. When the DMF was replaced by toluene, the acetylene **5** was still formed as the major product, albeit in a reduced yield of 48%. In addition to **5** we were also able to isolate the corresponding monocoupling product **18** in 15% yield. A similar result was obtained using THF as solvent, with both **5** (41%) and **18** (24%) being produced. These results showed that there is a solvent effect on the yield and product ratio and that DMF is the best solvent to use for the selective formation of the alkynyl phosphonate. We briefly examined the use of $Pd_2(dba)_3$[13] as the source of palladium, and while we were able to isolate the desired product **5** in

(10) When triethylamine was used in place of propylene oxide for this coupling, reduction of the 1,1-dibromo-1-alkene to the corresponding 1-bromo-1-alkene was observed. See: Abbas, S.; Hayes, C. J.; Worden, S. *Tetrahedron Lett.* **2000**, *41*, 3215 and references therein.

(11) For preparation of 1,1-dibromo-1-alkenes see: Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745.

(12) dppf = 1, 1′-Bis(diphenyl-phosphino)ferrocene.

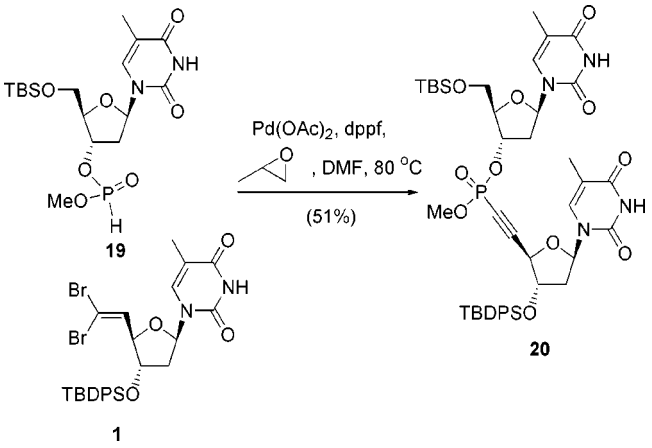
(13) No reaction of **4** was observed using the optimized monocoupling conditions of Shen[3] ($Pd_2(dba)_3$, TFP, toluene, 100 °C).

moderate yield (43%), higher yields and cleaner reaction mixtures were obtained with the use of $Pd(OAc)_2$.

With these results in hand we next performed the coupling reaction with a more extensive range of 1,1-dibromo-1-alkenes using the original "DMF" conditions (vide supra). As shown in Table 1, the coupling reaction appears to be tolerant of a range of functionality with the corresponding alkynylphosphonates being isolated in modest to good yields.[14] In the case of the furan-containing 1,1-dibromo-1-alkene **14**, the yield of the desired product **15** could be improved dramatically if the ligand was changed from dppf to TFP.[15] Under these modified conditions ($Pd(OAc)_2$ (0.2 equiv), TFP (0.8 equiv), dimethyl phosphite (2.0 equiv), propylene oxide (3.0 equiv)), DMF, 80 °C, 14 h), the isolated yield of **15** increased from 16% to 60%. The use of TFP as ligand in the coupling reactions of other substrates in Table 1 was examined, but this led to a reduction in yield in most cases. It is worth noting that, in their work, Shen et. al. observed ligand effects on the product distribution (i.e., alkyne formation vs monocoupling) when certain organostannanes were used as nucleophiles, but in their case TFP tended to favor monocoupling rather than alkyne formation.[16] It is not immediately apparent to us why the yield of the alkyne **15** is improved by the use of TFP while the yields of other couplings are reduced. Work is currently underway to explain this observation and provide a better mechanistic understanding of this process.[17]

Having shown that the thymidine-derived dibromide **1** was relatively well tolerated in the coupling with dimethyl phosphite, we next wondered if this methodology could be used to prepare the modified nucleotide dimer **20** by coupling with the more highly functionalized *H*-phosphonate **19**.[18] Pleasingly, the desired alkyne-containing thymidine dimer **20** was formed in 51% isolated yield (+12% recovered **1**)[19] when a mixture of **1** (1.0 equiv) and **19** (1.4 equiv) was exposed to the "DMF/dppf" coupling conditions (vide supra) (Scheme 3). Considering the complexity of this product, we believe that this result is particularly impressive and it clearly demonstrates the potential of this methodology to allow access to highly functionalized targets. We are currently examining the use of this coupling reaction for the synthesis of a range of other backbone-modified nucleic acids, and these results will be published in due course.

**Scheme 3**




In summary, we have developed a convenient method for the one-pot preparation of a range of alkynylphosphonates from the corresponding 1,1-dibromo-1-alkenes,[20] which is complementary to existing methodology.[21] In general, the best catalyst system for this transformation was found to be $Pd(OAc)_2$, dppf, propylene oxide, DMF, 80 °C. The reaction appears tolerant of a range of functional groups in both the 1,1-dibromo-1-alkene and *H*-phosphonate coupling partners, which should allow this methodology to find use in the synthesis of complex target molecules.

**Acknowledgment.** The authors thank the Nuffield Foundation (NUF-NAL) and the School of Chemistry, University of Nottingham, for financial support and The University of Nottingham for the provision of a Ph.D. studentship (M.L.).

**Supporting Information Available:** Characterization data for all alkynylphosphonate products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0066173

(14) All new compounds showed satisfactory $^1H$, $^{13}C$, $^{31}P$, IR, MS, and/or elemental analytical data.

(15) TFP = tris(2-furyl)phosphine.

(16) One exception to this was when trimethyl(phenyl)tin was used as the coupling partner. In this case alkyne formation was observed with a range of ligands, including TFP (see ref 3). The rate of transmetalation of the organostannane was proposed as the determining factor controling product selectivity in this process.

(17) We believe the mechanism of this reaction to be similar to that proposed by Shen (see ref 3).

(18) For synthesis, see ref 8b. The material was used as a 1:1 mixture of diastereoisomers at phosphorus.

(19) The product **20** was produced as a 1:1 mixture of diasteroisomers at phosphorus, which were readily separable by column chromatography using silica gel and ethyl acetate/pentane/methanol (10:10:1) as eluant.

(20) **Typical Procedure for the Preparation of Alkynylphosphonates:** A mixture of $Pd(OAc)_2$ (7 mg, 0.033 mmol) and dppf (36 mg, 0.066 mmol) in DMF (1 mL) was flushed with dry nitrogen and stirred at room temperature for 20 min. A solution of **1** (104 mg, 0.165 mmol) in DMF (1.5 mL), propylene oxide (35 $\mu$L, 0.50 mmol), and dimethyl phosphite (30 $\mu$L, 0.33 mmol) were added and the mixture was heated at 80 °C (bath temperature) for 14 h and then cooled to room temperature. Removal of the solvent in vacuo left a residue which was purified by column chromatography ($SiO_2$, EtOAc/pentane (3:1)) to afford **3** as a white solid (60 mg, 63%).

(21) See refs 5, 6, and 7 for alternative methodology.