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Copper-Mediated Cross-Coupling of *H*-Phosphonates with Vinyliodonium Salts: A Novel Very Mild Synthesis of 2-Arylvinylphosphonates

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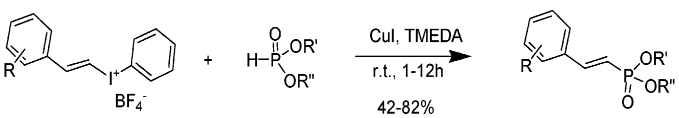
ABSTRACT



We report a novel, very mild, highly stereoselective preparation of 2-arylvinylphosphonates at room temperature that involves the copper iodide-mediated cross-coupling of *H*-phosphonates with vinyliodonium tetrafluoroborates.

Vinylphosphonates are of great importance in synthetic chemistry where they are commonly used in the preparation of carbocyclic and heterocyclic compounds.[1,2] They have been also extensively used in polymer sciences as additives or flame-retardants.[3] In medicinal chemistry, vinylphosphonates often exhibit interesting biological properties. This is the case for instance for nucleotide-[4] or polyisoprenoid-derived[5] vinylphosphonates. In a recent example, a series of substituted vinylphosphonates has been recognized in vitro as excellent matrix metalloproteinase (MMP-2) inhibitors with potential anti-cancer implications.[6]

Numerous methods are available for the synthesis of alkenylphosphonates but most of them suffer from several drawbacks: complexity, lack of stereoselectivity or drastic conditions not compatible with molecules containing sensitive functional groups.[1,2] Notable exceptions are recently developed transition metal-catalyzed carbon−phosphorus cross-coupling reactions such as the palladium-catalyzed coupling of diethyl vinylphosphonate with aryldiazonium salts[7] or with arylboronic acids[8] and the palladium-[9] or copper-catalyzed[10] coupling of readily available *H*-phosphonates with vinylhalides. Despite their relative mildness, these reactions are performed at relatively high (>50 °C) temperatures, and sometimes require the presence of strong bases.

We describe here a new very mild copper-catalyzed cross-coupling reaction between readily available vinyliodonium

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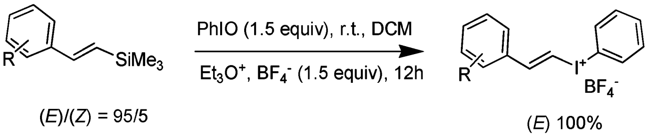
tetrafluoroborates[11] and *H*-phosphonates. The reaction proceeds well at room temperature to afford coupling products in good yields.[12,13] The starting (*E*)-vinyliodoniums **2a**−**e** were easily prepared from the vinyltrimethylsilyl derivatives **1a**−**d** as shown in Table 1 using a modified Ochiai's method.[11a]

Table 1. Preparation of (*E*)-2-Arylvinyl(phenyl)iodonium Tetrafluoroborates



(*E*)/(*Z*) = 95/5

1a-1h

(*E*) 100%

2a-2h

entry	R reactant	purification procedure[a]	product	yield[b] (%)
1	H, **1a**	A	**2a**	82
2	*o*-F, **1b**	A	**2b**	79
3	*o*-Me, **1c**	A	**2c**	80
4	*m*-OMe, **1d**	A	**2d**	66[c]
5[d]	*p*-CH=CHSiMe$_3$, **1e**	B	**2e**[e]	85
6	*p*-OMe, **1f**	C	**2f**	<20[f]
7	*p*-NO$_2$, **1g**	C	**2g**	0[g]
8	*o*-Br, **1h**	C	**2h**	0[g]

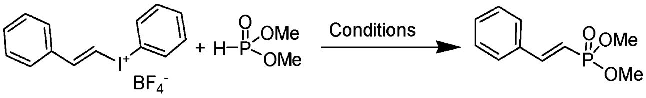
[a] A, trituration of the crude residue obtained after DCM evaporation in Et_2O then in Cy followed by SiO_2 column chromatography; B, washing of the precipitate with CH_2Cl_2; C, trituration in Cy. [b] Yield in product obtained after the purification procedure. [c] Accompanied by ca. 15% of impurities. [d] Three equivalents of PhIO and Et_3O^+ BF_4^- were used. [e] The bis-iodonium derivative was obtained (see Scheme 1). [f] Decomposed rapidly at room temperature. [g] Decomposed totally during the purification.

Silanes **1a**−**h**[14] consisted of *E*/*Z* mixtures (*E*/*Z, ca.* 95/5) but, as reported by Ochiai et al. for the preparation of **2a** (see the equation in Table 1) only the (*E*)-isomers reacted, leading to stereochemically pure (*E*)-iodonium salts.

Except for the bis-iodonium salt **2e** which readily precipitated, purification of tetrafluoroborates **2a**−**h** proved to be difficult. Ochiai's purification procedure, which involves precipitation of the salts by addition of diethyl ether and/or cyclohexane precipitation was not effective in our case. With the exception of **2d**, pure **2a**−**e** were obtained by trituration of the oily residue obtained after removal of the solvent at the end of the reaction with cyclohexane and diethyl ether followed by silica gel chromatography. Using these conditions, however, **2d** remained contaminated by ca. 15% of impurities.[15] Iodonium salts **2f**−**h** were too unstable to be purified and/or handled satisfactorily.

With the required iodonium salts **2a**−**e** in hand, we turned our attention to their coupling with various *H*-phosphonates, at room temperature, to afford 2-arylvinylphosphonates. As a model, we first studied the coupling of dimethyl phosphite with **2a** using the conditions recommended for coupling *H*-phosphonates with aryl iodides (presence of a base and DMF-containing solvent). In contrast to the latter reaction which proceeds under heating,[16] we were pleased to observe that, as shown by ^{31}P NMR monitoring, significant conversion already occurred after 4h at 20 °C (Table 2, entry 1), under $Pd(PPh_3)_4$ catalysis. Instead of investigating other palladium-based conditions, we switched to copper iodide-mediated conditions as previously reported for the cross-couplings (under heating) of simple vinylhalides to *H*-phosphonates.[10] After negative results using copper iodide either alone or in the presence of excess dimethylethylenediamine or *trans*-diaminocyclohexane as recommended[10b] (entries 2 and 3), we were pleased to discover that using tetramethylethylenediamine (TMEDA) resulted in an almost quantitative conversion after 4h at 20 °C (entry 4). Neither the addition of K_2CO_3 nor the presence of $Pd(PPh_3)_4$ as a second catalyst proved beneficial (entries 5 and 6) and, as expected, a blank experiment run with TMEDA alone yielded no traces of the desired vinylphosphonate (entry 7).

Table 2. Optimization of the Reaction Conditions[a]



(*E*) 100%

2a

(*E*) 100%

3a

entry	catalyst (equiv)	ligand	base	yield[b] (%)
1	$Pd(PPh_3)_4$ (0.1)		K_2CO_3	20
2	CuI (0.3)			0
3	CuI (0.3)	L[c]		0
4	CuI (0.3)	TMEDA		>95 (82)
5	CuI (0.3)	TMEDA	K_2CO_3	>95 (80)
6	CuI (0.3) $Pd(PPh_3)_4$ (0.1)	TMEDA	K_2CO_3	10
7		TMEDA		0

[a] Reaction conditions: iodonium **2a** (1.5 equiv), room temperature, DMF/THF (1/4), 4 h. [b] Conversion in ^{31}P NMR, isolated yield of **3a** after chromatography in brackets. [c] L = *trans*-diaminocyclohexane or dimethylethylenediamine.

Finally, the reaction of (2-iodo-vinyl)-benzene with dimethyl phosphite in the presence of $Pd(PPh_3)_4$ and K_2CO_3 at room temperature (same conditions as in Table 2, entry

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[11] (a) Ochiai, M.; Sumi, K.; Takaoka, Y.; Kunishima, M.; Nagao, Y.; shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095−4112. (b) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274−285.

[12] Hypervalent iodine derivatives have been successfully used in various transition metal-catalyzed couplings near room temperature but, to the best of our knowledge, the method has not been applied to the preparation of vinylphosphonates (a) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Ho, P.-S. *J. Org. Chem.* **1996**, 61, 4720−4724. (b) Moriarty, R. M.; Epa, W. R. *Tetrahedron Lett.* **1992**, *33*, 4095−4098.

[13] Coupling of hypervalent iodine derivatives with sodium dialkylphosphonates has been used for the preparation of alkynyl- and arylphosphonates. The reaction proceeds at 70−90 °C in DMF. (a) Liu, Z.-D.; Chen, Z.-C. *Synthesis* **1993**, 373−374. (b) Zhang, J.-L.; Chen, Z.-C. *Synth. Commun*. **1998**, *28*, 175−179.

[14] Vinyltrimethylsilyl derivatives are directly issued from the DIBAL-*H* reduction of the corresponding alcynyl compounds as described previously: Eisch, J. J.; Foxton, M. W. *J. Org. Chem*. **1971**, *36*, 3520−3526.

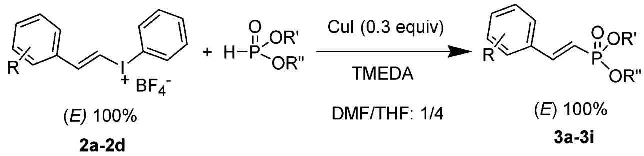
[15] The presence of these impurities did not appear as an handicap when iodonium **2d** was engaged in a coupling reaction with dimethyl phosphite (Table 3, entry 9).

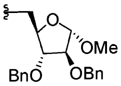
[16] (a) Hirao, T.; Masunaga, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909−913. (b) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Synthesis* **198**1, 56−57.

1), was examined. After 24 h, only very small amounts (ca. 10%) of coupling product was formed as evidenced by ^{31}P NMR of the reaction mixture. The starting iodide was still present as a major compound along with unidentified decomposition material. Attempted coupling of (2-iodovinyl)benzene with dimethyl phosphite under CuI catalysis (same conditions as in Table 2, entry 4) failed completely.

Having established the best conditions for the coupling of **2a** and dimethyl phosphite, we next examined whether our findings could be extended to other *H*-phosphonates and iodonium salts. The results of these experiments are reported in Table 3. With the exception of diphenylester **3e** (entry 5) which partially decomposes upon chromatrography on silicagel, reaction of **2a** with a series of *H*-phosphonates generally afforded good yields of coupling products (Table 3, entries 1−6). Comparison of entries 1, 2 and 3 shows that the rate of the coupling reaction gradually drops when increasing the size of the alkyl groups in the *H*-phosphonates; for R′ = R″ = butyl, the reaction was best run at 35 °C. The *arabino*-furanosyl derivative **3f** was obtained as a 1:1 mixture of isomers at the phosphorus level, which could not be separated on SiO$_2$ (preparative plates).

Table 3. Room Temperature Synthesis of Dialkyl (*E*)-2-Arylvinylphosphonates[a]



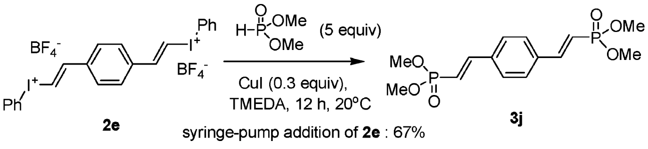
entry	iodo-nium	R’	R”	time (h)	yield%[b] **product**
1	**2a**	Me	Me	4	82 **3a**
2[c]	**2a**	Et	Et	12	79 **3b**
3[c,d]	**2a**	*n*-Bu	*n*-Bu	15	71 **3c**
4	**2a**	Bn	Bn	4	63 **3d**
5	**2a**	C$_6$H$_5$	C$_6$H$_5$	1	42[e] **3e**
6	**2a**	Me		4	64 **3f**
7[f]	**2b**	Me	Me	4	66 **3g**
8[f]	**2c**	Me	Me	4	76 **3h**
9	**2d**	Me	Me	4	83 **3i**

[a] Reaction conditions: iodonium (1.5 equiv), room temperature. [b] Isolated yield of product after chromatography. [c] 2.5 equiv of iodonium. [d] 35 °C. [e] Released PhOH during the purification. [f] Slow syringe-pump addition.

We also examined the coupling-reaction of iodoniums **2b**-**2d** with dimethyl phosphite (Table 3, entries 7−9). For the preparation of phosphonates **3g** and **3h**, much better yields were obtained by slow (syringe-pump) addition of the starting iodoniums **2b** and **2c** to the reaction mixture.[17]

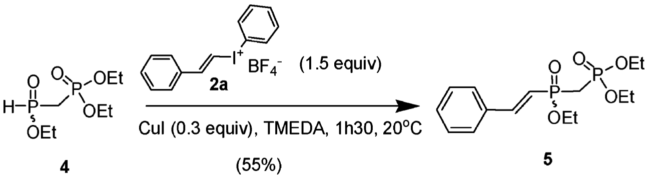
Slow addition of the bis-iodonium salt **2e** to a large excess of dimethyl phosphite over a period of 4h afforded diphosphonate **3j** in good yield (Scheme 1). Here again, failure to use high dilution conditions led to a poor (<10%) yield of the desired coupling product along with a complex mixture of unidentified polar compounds.

Scheme 1



Our coupling conditions were also tested on the more elaborated *H*-phosphinylphosphonate triethylester **4** for which a simple preparation was recently described by us (Scheme 2).[18] The reaction proceeded smoothly and rapidly at room temperature to furnish, after chromatographic purification, the vinylic phosphinate **5** in good yield.

Scheme 2



Overall, these studies demonstrated the broad scope of the coupling reaction and we decided to apply the method to more complex and functionalized systems. A sensitive mixed phosphite ester closely related to **7**, featuring a protected adenosylated moiety, has been previously reported not to stand the reaction conditions during attempted coupling with an activated mesylate.[19] The compound’s instability already appeared when purifying **7** (prepared from **6** and methyldichlorophosphite in the presence of an excess of lutidine): we could not get an isolated yield higher than 45% because

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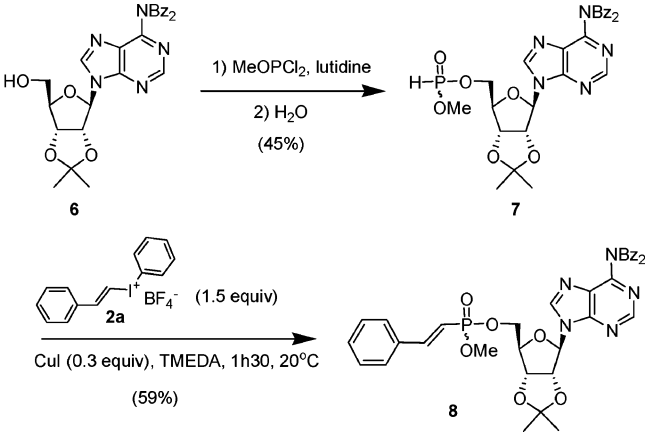
(17) Without this precaution, yields in vinylphosphonates were below 45% and a substantial amount (10-20%) of the corresponding alkynyl phosphonates ArC≡CP(O)(OMe)$_2$ was also isolated. These latter compounds probably resulted from a copper-catalyzed coupling of dimethyl phosphite on the alkynes issued from the elimination of PhI from the starting iodoniums **2b** or **2c**. Indeed, in a blank experiment ran on dimethyl phosphite and phenylacetylene, we observed the formation of 15% of dimethyl 2-phenylethynylphosphonate after 4 h at room temperature under the conditions selected for coupling iodonium salts.

(18) Bisseret, P.; Eustache, J. *Tetrahedron Lett*. **2001**, *42*, 8451−8453.

(19) Salaski, E. J.; Maag, H. *Synlett* **1999**, *S1*, 897−900. The coupling of a mixed phosphite ester bearing a protected adenosyl moiety and a trimethylsilylethoxy group with a primary mesylate by NaH treatment failed.

Scheme 3



of the tendency of **7** to revert to **6**. This instability led to very poor yields in coupling experiments performed at room temperature using Pd(PPh$_3$)$_4$ as a catalyst (see conditions Table 2, entry 1). In contrast, using our copper-catalyzed conditions, the expected pair of phosphorus diastereomers **8** was obtained in good yield and in less than 2h at 20 °C. Interestingly, and in contrast to phosphonates **3f**, the two diastereomers could be cleanly separated by chromatography over silica gel (Scheme 3).

In conclusion, we have established a novel, general method for the efficient preparation of 2-aryl-vinylphosphonates based on the coupling of hypervalent vinyliodonium salts to *H*-phosphonates.

Considering the very mild conditions of the reaction, it should be useful for the preparation of polyfunctionalized derivatives as illustrated by the synthesis of **8**.

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Supporting Information Available: Experimental procedures and characterization for iodonium salts and arylphosphonates. This material is available free of charge via the Internet at http://pubs.acs.org.

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