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The Preparation of Heterobiaryl Phosphonates *via* the Stille Coupling Reaction

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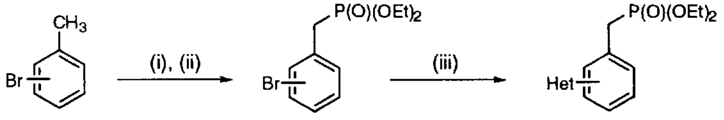
Abstract: The Stille cross-coupling reaction between various heteroarylstannanes and substituted bromo-benzylphosphonates was used to prepare heterobiaryl phosphonates in moderate to good yields. Copyright © 1996 Elsevier Science Ltd

The biaryl group is an important structural sub-unit which is found in many areas of medicinal chemistry and which also occurs in many natural products.[1] The preparation of biaryl and heterobiaryl compounds is best accomplished by one of the methodologies based on the cross-coupling of an aryl/heteroaryl metalloid with an aryl bromide, iodide or triflate under the influence of a palladium (0) catalyst.[2] Such cross-coupling reactions have become increasingly popular since the presence of delicate functionality in one or both partners is often tolerated. The presence of groups capable of further modification in either partner makes the formation of the aryl-aryl bond a strategically attractive process.

We identified a series of heterobiaryls as potentially interesting sub-units to be incorporated into biologically active nuclei *via* the Wittig or the Wadsworth-Horner-Emmons reaction. Therefore, we required a series of phosphorus containing biaryls and, in particular, we chose phosphonates **3** (scheme 1) as suitable targets on account of their ease of purification when compared to the corresponding phosphonium salts. From a medicinal chemistry point of view, phosphonic acid derivatives such as **3** are also interesting since the phosphonate group can be regarded as a bioisostere of the carboxylic acid group.[3]



1a *ortho*
1b *meta*
1c *para*

2a-c

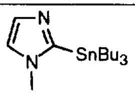
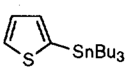
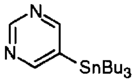
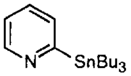
3

conditions: (i) NBS / $(^tBuO)_2$ (cat) / CCl_4 / Δ; (ii) $P(OEt)_3$ / Δ;
(iii) $PdCl_2(PPh_3)_2$ / CH_3CN / Δ / $HetSnBu_3$

Scheme 1

The three isomeric bromobenzylphosphonates **2a-c** were easily prepared from the corresponding bromotoluenes **1a-c** *via* side-chain bromination followed by Arbuzov reaction with triethyl phosphite and their subsequent reaction with a variety of heteroaryl stannanes under palladium catalysis was studied as outlined in Scheme 1. The heteroarylstannanes were prepared according to literature procedures.[4] The results of the cross- coupling reactions are collected in the Table 1.

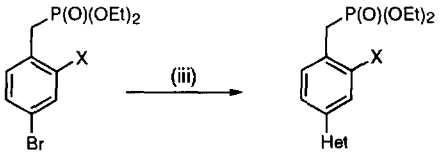
Table 1

Entry	phosphonate	stannane	yield of biaryl
1	2a		24%
2	2b	..	55%
3	2c	..	69%
4	2b		56%
5	2b		72%
6	2c	..	64%
7	2b		43%
8	2b	..	35%

for conditions see note 5

We found that the reaction proceeded best in refluxing acetonitrile, neither toluene nor DMF proved to be suitable solvents. In general, the reaction was complete in 6-18h depending on the stannane. In the case of the couplings with the stannyl-thiophene, the portionwise addition of the catalyst every 2h was found to be necessary owing to the continuous slow deposition of palladium metal. The preference for the use of palladium (II) catalysts in couplings between heteroaryl stannanes with aryl bromides is reported in the literature and it was apparent that $PdCl_2(PPh_3)_2$ was superior to $Pd(PPh_3)_4$ in this study.[6] In general, the yields ranged from moderate with the 2-pyridyl stannane (Entries 7 and 8) to good in the case of the 2-*N*-methyl-imidazolyl- and 5-pyrimidyl- species (Entries 2-3 and 5-6, respectively). The low yield encountered in the reaction of the 2-*N*-methyl-imidazolyl stannane with *ortho*-bromobenzylphosphonate **2a** may be due to steric factors to which the Stille reaction has been reported to be sensitive.[7]

The method was extended to the chloro and nitro substituted bromobenzylphosphonates **4** and **5** which were prepared and used analogously to **2a-c** (scheme 2).



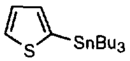
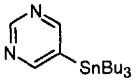
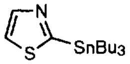
4 X = Cl
5 X = NO_2

6

Scheme 2

The results of the cross-couplings with these compounds are collected in Table 2. It was found that these phosphonates reacted smoothly with 2-tributylstannyl-thiophene, -thiazole and 5-tributylstannyl-pyrimidine and as anticipated the couplings proceeded without interference of the phosphonate group to give good yields of coupled products (table 2).

Table 2

Entry	phosphonate	stannane	yield of biaryl
1	4		69%
2	5		65%
3	5		63%

for conditions see note 5

In summary, the palladium (0) catalysed cross-coupling reaction between heteroarylstannanes and variously substituted bromobenzylphosphonates has been found to give useful yields of the corresponding heterobiaryl compounds which are suitable substrates for further elaboration.

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References and Notes

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5. *Typical conditions:* A mixture of 2-tributylstannyl-*N*-methylimidazole (290mg, 0.78mmol), diethyl-p-bromobenzyl phosphonate **2a** (188mg, 0.61mmol) and $PdCl_2(PPh_3)_2$ (11.2mg) in dry acetonitrile (5ml) under N_2 was refluxed for 6.5h. The mixture was cooled, diluted with acetonitrile and washed with petroleum ether (40-70) (5 x 25ml), solvent removed and the residual oil chromatographed on silica to give 147mg (78%) diethyl-*p*-(2-*N*-methylimidazolyl)benzylphosphonate as a colourless oil. All compounds gave satisfactory spectroscopic analyses.
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