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Synthesis of isoindol-1-ylphosphonate derivatives via Pd(0)-catalyzed reaction of α-amino (2-alkynylphenyl) methylphosphonate with aryl iodide

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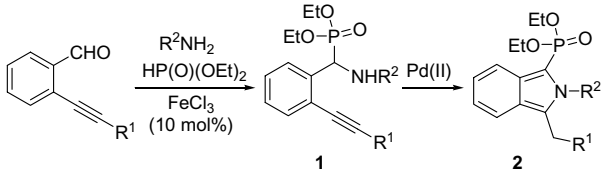
Abstract—α-Amino (2-alkynylphenyl) methylphosphonate, which was generated from 2-alkynyl benzaldehyde, amine, and diethyl phosphate, reacted with aryl iodide at room temperature in the presence of catalytic amount of $Pd_2(dba)_3$ and DABCO in acetone, leading to the desired isoindol-1-ylphosphonate derivatives in good to excellent yields.

As a privileged fragment, the isoindole core is an ubiquitous subunit in many natural and synthetic products with remarkable biological activities. Members of this family have wide applications in medicinal chemistry, being used as antibiotic and antitumor agents.[1] On the other hand, considerable attention has been paid to α-amino phosphonic acids, their phosphonate esters, and short peptides incorporating this unit, which are excellent inhibitors of a wide range of proteolytic enzymes.[2] In addition, α-amino phosphonate derivatives have broad application due to their antibacterial[3] and antifungal[4] activity, and as inhibitors of phosphatase activity.[5] Preparation of phosphono-substituted heterocyclic compounds is also of great interest largely because of their possible relevance to the mechanism of certain enzymatic events.[6] To the best of our knowledge, there are few reports for the synthesis of phosphonylated isoindoles.[7] Recently, we described an efficient synthesis of phosphonylated isoindoles via palladium(II)-catalyzed cyclization and [1,5]-H shift from α-amino (2-alkynylphenyl) methylphosphonate, which was synthesized from 2-alkynyl benzaldehyde, amine, and diethyl phosphate (Scheme 1).[7a] Meanwhile, Stevens also reported that, when *o*-ethynylbenzyl α-aminophosphonates were heated under microwave conditions, a rearrangement occurred which resulted in the formation of phosphonylated isoindoles.[7b]



Scheme 1.

The rearrangement consisted of a 5-*exo*-*dig* cyclization followed by a [1,3]-alkyl shift and finally aromatization. In light of our continuous interest in natural product-like compounds,[7a,8] we required an efficient method to introduce more diversity into the phosphonylated isoindole scaffold, with a hope of finding more active hits or leads for our particular biological assays.[9] Herein, we disclose our efforts for the synthesis of isoindol-1-ylphosphonate derivatives via Pd(0)-catalyzed reaction of α-amino (2-alkynylphenyl) methylphosphonate with aryl iodide.

As outlined in Scheme 2, in the presence of Pd(0) and aryl iodide, R^3 could be easily installed in the isoindole scaffold, which undergoes 5-*exo*-cyclization[10] and subsequent [1,5]-H shift. Therefore, we started to investigate

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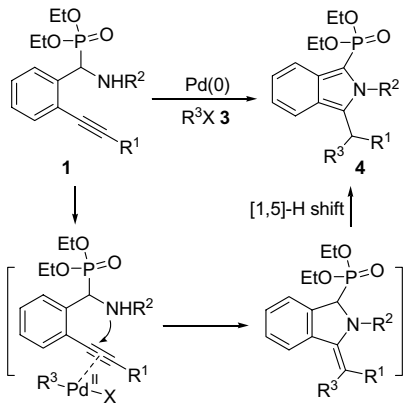


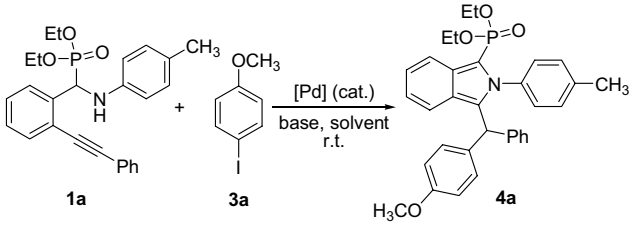
Scheme 2.

the Pd(0)-catalyzed reaction of α-amino (2-alkynylphenyl) methylphosphonate with aryl iodide. Initial studies were aimed at finding the optimal reaction conditions for this reaction. Our investigation began with the reactions of α-amino (2-alkynylphenyl) methylphosphonate **1a** with 1-iodo-4-methoxybenzene **3a** (Table 1).

From Table 1, it was found that only trace amount of the product was detected in the presence of $Pd(PPh_3)_4$, when the reaction was performed in DMF (Table 1, entry 1). To our delight, 52% yield of desired product **4a** was generated when $Pd_2(dba)_3$ (10 mol %) was utilized as catalyst and K_2CO_3 was used as base (Table 1, entry 2). The product was fully characterized by ^1H, ^{13}C, ^{31}P NMR, mass and elemental analysis. The ^{31}P NMR shift around 10 ppm indicates that the phosphorus is attached to an sp^2 carbon.[7,11] Decreasing the amount of catalyst to 5 mol % gave the similar result, while the reaction was retarded when 2 mol % of $Pd_2(dba)_3$ was employed in this reaction. Inferior results were observed when Pd(II)/PPh_3 was used in the reaction (Table 1, entries 5–8). Further studies revealed that DABCO was the best choice of base (Table 1, entry 13). For the amount of base used in the reaction, 5 equiv of DABCO was the ideal. Acetone afforded the best result among the solvents screened (86% yield, Table 1, entry 16).

To demonstrate the generality of this method, we next investigated the scope of this reaction and the results are summarized in Table 2. From Table 2, we found that optimised conditions allowed us to perform a broad range of α-amino (2-alkynylphenyl) methylphosphonate **1** with aryl iodide **3**. Synthetically, all these reactions illustrated in Table 2 went to completion at room temperature within 48 h, and for most of the cases, the desired products were afforded in good to excellent yields. Aryl iodides with electron-donating or electron-withdrawing group attached on the aromatic ring were all good partners in this transformation. For example, compound **1b** reacted with 1-iodo-4-methoxybenzene **3a** leading to the corresponding product **4b** in 90% yield (Table 2, entry 2), and 79% yield of product **4l** was obtained when 1-fluoro-4-iodobenzene **3c** was utilized in the reaction (Table 2, entry 12).

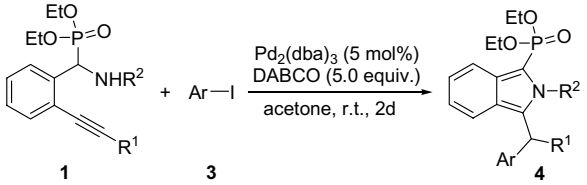
Table 1. Screening conditions for palladium-catalyzed reaction of α-amino (2-alkynylphenyl) methylphosphonate **1a** with aryl iodide **3a**



Entry	[Pd]	Base	Solvent	Yield[a] (%)
1	$Pd(PPh_3)_4$ (10 mol %)	K_2CO_3	DMF	Trace
2	$Pd_2(dba)_3$ (10 mol %)	K_2CO_3	DMF	52
3	$Pd_2(dba)_3$ (5 mol %)	K_2CO_3	DMF	51
4	$Pd_2(dba)_3$ (2 mol %)	K_2CO_3	DMF	10
5[b]	$PdCl_2$ (5 mol %)	K_2CO_3	DMF	Trace
6[b]	$Pd(OAc)_2$ (5 mol %)	K_2CO_3	DMF	Trace
7[b]	$PdCl_2(PPh_3)_2$ (5 mol %)	K_2CO_3	DMF	Trace
8[b]	$PdCl_2(PhCN)_2$ (5 mol %)	K_2CO_3	DMF	14
9	$Pd_2(dba)_3$ (5 mol %)	NaOAc	DMF	Trace
10	$Pd_2(dba)_3$ (5 mol %)	Na_2CO_3	DMF	Trace
11	$Pd_2(dba)_3$ (5 mol %)	Cs_2CO_3	DMF	Trace
12	$Pd_2(dba)_3$ (5 mol %)	Et_3N	DMF	Trace
13	$Pd_2(dba)_3$ (5 mol %)	DABCO	DMF	69
14	$Pd_2(dba)_3$ (5 mol %)	DABCO	DMSO	13
15	$Pd_2(dba)_3$ (5 mol %)	DABCO	CH_3CN	31
16	$Pd_2(dba)_3$ (5 mol %)	DABCO	Acetone	86
17	$Pd_2(dba)_3$ (5 mol %)	DABCO	DCE	70
18	$Pd_2(dba)_3$ (5 mol %)	DABCO	THF	65
19	$Pd_2(dba)_3$ (5 mol %)	DABCO	Toluene	18

[a] Isolated yield based on α-amino (2-alkynylphenyl) methylphosphonate **1a**.
[b] In the presence of PPh_3 (10 mol %).

Table 2. Synthesis of isoindol-1-ylphosphonate derivatives via Pd(0)-catalyzed reaction of α-amino (2-alkynylphenyl) methylphosphonate with aryl iodide[12]



1 3 4

Entry	R^1/ R^2	Ar	Product	Yield[a] (%)
1	C_6H_5/4-MeC_6H_4 (**1a**)	4-MeOC_6H_4 (**3a**)	**4a**	86
2	C_6H_5/4-MeOC_6H_4 (**1b**)	4-MeOC_6H_4 (**3a**)	**4b**	90
3	C_6H_5/C_6H_5 (**1c**)	4-MeOC_6H_4 (**3a**)	**4c**	66
4	C_6H_5/4-FC_6H_4 (**1d**)	4-MeOC_6H_4 (**3a**)	**4d**	78
5	C_6H_5/4-ClC_6H_4 (**1e**)	4-MeOC_6H_4 (**3a**)	**4e**	48
6	C_6H_5/4-MeC_6H_4 (**1a**)	C_6H_5 (**3b**)	**4f**	88
7	C_6H_5/4-MeOC_6H_4 (**1b**)	C_6H_5 (**3b**)	**4g**	90
8	C_6H_5/C_6H_5 (**1c**)	C_6H_5 (**3b**)	**4h**	86
9	C_6H_5/4-FC_6H_4 (**1d**)	C_6H_5 (**3b**)	**4i**	94
10	C_6H_5/4-ClC_6H_4 (**1e**)	C_6H_5 (**3b**)	**4j**	80
11	C_6H_5/4-MeC_6H_4 (**1a**)	4-FC_6H_4 (**3c**)	**4k**	72
12	C_6H_5/4-MeOC_6H_4 (**1b**)	4-FC_6H_4 (**3c**)	**4l**	79
13	C_6H_5/C_6H_5 (**1c**)	4-FC_6H_4 (**3c**)	**4m**	80
14	C_6H_5/4-FC_6H_4 (**1d**)	4-FC_6H_4 (**3c**)	**4n**	92
15	C_6H_5/4-ClC_6H_4 (**1e**)	4-FC_6H_4 (**3c**)	**4o**	88

[a] Isolated yield based on α-amino (2-alkynylphenyl) methylphosphonate **1**.

In summary, the reaction described here represents a highly efficient and practical route to isoindol-1-ylphosphonate derivatives. It is likely that the efficiency of introducing diversity combined with the operational simplicity of the present process will make it attractive for library construction. The focused library generation and screening for biological activity of these small molecules are under investigation in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.062.

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12. General procedure for the synthesis of isoindol-1-ylphosphonate derivatives via Pd(0)-catalyzed reaction of α-amino (2-alkynylphenyl) methylphosphonate with aryl iodide: A solution of α-amino (2-alkynylphenyl) methylphosphonate **1** (0.2 mmol), aryl iodide **3** (1 mmol, 5 equiv), $Pd_2(dba)_3$ (0.01 mmol, 5 mol %), DBACO (1.0 mmol, 5.0 equiv) in acetone (1.0 mL) was stirred at room temperature under N_2 for two days. After completion of reaction as indicated by TLC, the solvent was evaporated under reduced pressure. The residue was quenched with water (10 mL) and extracted with EtOAc (2×10 mL), then dried by anhydrate Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **4**. Selected examples: Diethyl 3-((4-methoxyphenyl)(phenyl)methyl)-2-*p*-tolyl-2*H*-isoindol-1-ylphosphonate (**4a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, $J = 6.8$ Hz, 6H), 2.43 (s, 3H), 3.78 (s, 3H), 3.80–4.01 (m, 4H), 5.41 (s, 1H), 6.77 (d, $J = 8.8$ Hz, 2H), 6.80–6.86 (m, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 6.96–7.02 (m, 4H), 7.08–7.13 (m, 1H), 8.17 (d, $J = 8.8$ Hz, 2H), 7.20–7.25 (m, 3H), 8.13 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 16.1, 21.3, 48.2, 55.2, 61.4, 61.5, 107.8 (d, $J = 233.6$ Hz), 113.6, 120.5, 120.9, 121.3, 122.7, 124.1, 126.6, 128.3, 128.8, 129.0, 130.1, 133.1, 133.4, 134.4, 135.5, 139.2, 141.8, 158.2; ^{31}P NMR (161 MHz, $CDCl_3$) δ 10.25; MS: *m*/*z* 540.2 (M^++1); Elemental Anal. Calcd (%) for $C_{33}H_{34}NO_4P$:C, 73.45; H, 6.35; N, 2.60. Found: C, 73.25; H, 6.17; N, 2.44. Diethyl 2-(4-methoxyphenyl)-3-((4-methoxyphenyl)(phenyl)methyl)-2*H*-isoindol-1-ylphosphonate (**4b**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, $J = 6.4$ Hz, 6H), 3.77 (s, 3H), 3.85 (s, 3H), 3.86–4.05 (m, 4H), 5.43 (s, 1H), 6.76–6.81 (m, 4H), 6.86–6.90 (m, 4H), 6.96–7.03 (m, 4H), 7.08–7.12 (m, 1H), 7.20–7.23 (m, 3H), 8.13 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 16.2, 48.3, 55.2, 55.4, 61.4, 61.5, 108.1 (d, $J = 233.6$ Hz), 113.2, 113.6, 120.5, 120.8, 121.3, 122.7, 124.1, 126.6, 128.3, 129.0, 129.6, 130.1, 130.8, 132.9, 133.4, 134.6, 141.7, 158.2, 158.9; ^{31}P NMR (161 MHz, $CDCl_3$) δ 10.33; MS: *m*/*z* 556.2 (M^++1); Elemental Anal. Calcd (%) for $C_{33}H_{34}NO_5P$: C, 71.34; H, 6.17; N, 2.52. Found: C, 71.39; H, 6.08; N, 2.45. Diethyl 3-((4-methoxyphenyl)(phenyl)methyl)-2-phenyl-2*H*-isoindol-1-ylphosphonate (**4c**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, $J = 7.3$ Hz, 6H), 3.78 (s, 3H), 3.80–3.98(m, 4H), 5.40 (s, 1H), 6.77 (d, $J = 8.3$ Hz, 2H), 6.81–6.82 (m, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.95–6.97 (m, 2H), 7.09–7.14 (m, 3H), 7.21–7.24 (m, 3H), 7.36–7.40 (m, 2H), 7.47 (t, $J = 7.8$ Hz, 1H), 8.13 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 16.1, 48.3, 55.2, 61.5, 61.6, 107.9 (d, $J = 233.6$ Hz), 113.7, 120.5, 120.9, 121.5, 122.7, 124.3, 126.6, 128.2, 128.3, 128.7, 129.0, 129.3, 130.1, 133.1, 133.3, 134.3, 138.1, 141.7, 158.3; ^{31}P NMR (161 MHz, $CDCl_3$) δ 9.95; MS: *m*/*z* 526.2 (M^++1); Elemental Anal. Calcd (%) for $C_{32}H_{32}NO_4P$: C, 73.13; H, 6.14; N, 2.67. Found: C, 72.85; H, 6.19; N, 2.71. Diethyl 2-(4-fluorophenyl)-3-((4-methoxyphenyl)(phenyl)methyl)-2*H*-isoindol-1-ylphosphonate (**4d**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, $J = 6.8$ Hz, 6H), 3.78 (s, 3H), 3.83–4.00 (m, 4H), 5.39 (s, 1H), 6.75–6.80 (m, 4H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.95–6.97 (m, 2H), 7.06 (d, $J = 6.8$ Hz, 4H), 7.10 (t, $J = 7.6$ Hz, 1H), 7.22–7.25 (m, 3H), 8.11 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 16.1, 48.4, 55.2, 61.5, 61.6, 108.3 (d, $J = 233.6$ Hz), 113.7, 115.1, 120.4, 120.8, 121.6, 122.8, 124.4, 126.7, 128.4, 128.9, 130.1, 130.4, 132.9, 133.1, 134.1, 134.4, 141.5, 158.3, 162.7 (d, $J = 247.9$ Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 9.92; MS: *m*/*z* 544.2 (M^++1); Elemental Anal. Calcd (%) for $C_{32}H_{31}FNO_4P$: C, 70.71; H, 5.75; N, 2.58. Found: C, 70.47; H, 5.58; N, 2.43. Diethyl 2-(4-chlorophenyl)-3-((4-methoxyphenyl)(phenyl)-methyl)-2*H*-isoindol-1-ylphospho-nate (**4e**). ^{1}H NMR (400 MHz,$CDCl_3$) δ 1.17 (t, $J = 6.8$ Hz, 6H), 3.78 (s, 3H), 3.87–4.01 (m, 4H), 5.38 (s, 1H), 6.77–6.80 (m, 4H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.94–6.96 (m, 2H), 7.01–7.04 (m, 2H), 7.10–7.14 (m, 1H), 7.22–7.25 (m, 3H), 7.33–7.36 (m, 2H), 8.10 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 16.1, 48.4, 55.1, 61.5, 61.6, 108.2 (d, $J = 232.6$ Hz), 113.7, 120.4, 120.8, 121.6, 122.8, 124.4, 126.7, 128.4, 128.9, 129.9, 130.0, 132.9, 133.0, 134.2, 135.2, 136.6, 141.4, 158.3; ^{31}P NMR (161 MHz, $CDCl_3$) δ 9.81; MS: *m*/*z* 560.2 (M^++1); Elemental Anal. Calcd (%) for $C_{32}H_{31}ClNO_4P$: C, 68.63; H, 5.58; N, 2.50. Found: C, 68.71; H, 5.45; N, 2.39.