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A new and direct approach to functionalized biaryl α-ketophosphonic acids via aqueous Suzuki coupling on solid support

Xianfeng Li,* Anna Katrin Szardenings, Christopher P. Holmes, Liang Wang, Ashok Bhandari, Lihong Shi, Marc Navre, Larry Jang and J. Russell Grove

Affymax, Inc., 4001 Miranda Avenue, Palo Alto, CA 94304, USA

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Abstract—A new method for the synthesis of functionalized biaryl α-ketophosphonic acids has been developed. The key step involves the use of sodium bromobenzoyl phosphonates to react with polymer-bound boronic acids via microwave-assisted aqueous Suzuki coupling. This approach provides rapid access to a wide range of diverse biaryl analogues containing an α-ketophosphonic acid moiety.

α-Ketophosphonic acids (Fig. 1) exhibit a wide range of biological activities. Kluger et al. first reported that simple aliphatic α-ketophosphonic acids were competitive inhibitors of pyruvate dehydrogenase,[1] and pyruvate oxidase.[2] Later, Tao et al. found peptidic α-ketophosphonic acids exhibited inhibitory activity against human calpain I.[3] Aliphatic α-ketophosphonic acids are also biologically active in calcium-related disorders such as hydroxyapatite formation and dissolution.[4] Moreover, α-ketophosphonic acid group represents a non-hydrolyzable phosphate mimetic that would be useful for designing inhibitors to target the phosphate binding sites of therapeutic enzymes.[5] However, the papers that have been published so far include only simple and isolated examples. There is a lack of methods for the synthesis of diverse and complex α-ketophosphonic acids, which has thus far limited their utilization in biological studies.

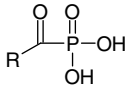

Figure 1. α-Ketophosphonic acids.

The precursors of α-ketophosphonic acids are the corresponding diesters. Since the carbonyl group of an α-ketophosphonate diester is highly activated, α-ketophosphonates containing C(O)–P bonds are known to be highly labile and decompose readily into carboxylic acids and dialkyl phosphonates.[6–9] α-Ketophosphonates have been shown to be susceptible to nucleophilic attack by alcohols, thiols, amines, and enolates.[6–9] These properties make them versatile intermediates, but also very difficult to handle and purify. α-Ketophosphonates are usually prepared by Michaelis–Arbuzov reaction between acid chlorides with trialkyl phosphites[10] or by the oxidation of α-hydroxyphosphonates.[11] It has been known that the Michaelis–Arbuzov reaction works well only for the less complex acid chlorides. The oxidation of α-hydroxyphosphonates tends to work well for isolated examples, but not usually general for a range of diverse substrates.

As part of our efforts to identify novel PTP inhibitors,[12] we became interested in the synthesis and evaluation of α-ketophosphonic acids. This class of compounds contains an electron-deficient carbonyl group, which provides an opportunity of interacting directly with the active site cysteine residue and thus might serve as mechanism-based inhibitors of PTPs.[13] In addition, the

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* Corresponding author at address: Galileo Pharmaceuticals, Inc., Santa Clara, CA 95054, USA. Tel.: +1 408 654 5830x228; fax: +1 408 654 5832; e-mail: xli@galileopharma.com

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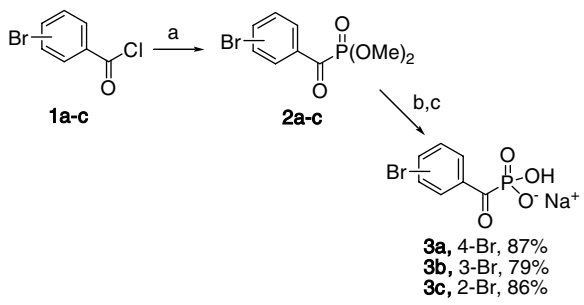
inductive effect of the carbonyl group on phosphonate acidity results in low pK_a values (calcd pK_a 0.8 and 5.1), indicating their good binding ability to the highly cationic active site of PTPs. It has been shown by Breuer et al. that α-ketophosphonic acids are far more stable than their corresponding esters,[8] presumably due to the phosphonate dianion being a very poor leaving group. Thus, we envisioned that α-ketophosphonic acids (or their salts) could be used directly as precursors to construct diverse and complex analogues. Since biaryl scaffolds have proven to be good templates for designing small molecule PTP inhibitors,[12,14] we chose to display α-ketophosphonic acid group on biaryl scaffolds via Pd-assisted Suzuki coupling chemistry.[15] In particular, we wanted to develop a solid-phase approach that would allow for the rapid synthesis of analogues with various substituents around a biaryl scaffold.

As outlined in Scheme 1, sodium bromobenzoyl phosphonates **3a**–**c** were prepared from the reaction of bromobenzoyl chlorides **1a**–**c** (*para*, *meta*-, and *ortho*-) with trimethyl phosphite in the absence of any solvent to give dimethyl esters **2a**–**c**. Subsequent treatment of the diesters with TMSBr afforded the acids. After removal of excess TMSBr, addition of one equivalent of sodium hydroxide in methanol precipitated **3a**–**c** from the reaction mixture as sodium salts. The salt forms **3a**–**c** are stable and easy to handle, and thus could be conveniently used in a parallel synthesis approach. More importantly, the formation of sodium salts greatly simplifies the purification and allows the easy preparation of these building blocks on multi-gram scale. Compounds **3a**–**c** showed a high level of purity according to HPLC, ^{1}H, and ^{31}P NMR analysis.[16]

With a set of building blocks **3a**–**c** available, we investigated the Suzuki coupling conditions in solution by varying the reaction parameters (i.e., catalyst, base, solvent, and temperature). This led to the identification of a general set of conditions for the coupling reactions (boronic acid/**3a**–**c** = 2/1, 5% $Pd(OAc)_2$, a mixed solvent of 10% aqueous K_2CO_3 and CH_3CN (2:1 v/v), microwave, 10 min). The combination of aqueous potassium carbonate and acetonitrile was chosen as a solvent system for the coupling reaction, because both reactants are very polar in nature and have good water solubility. Microwave irradiation[17,18] was found to give good results for $Pd(OAc)_2$ catalyzed coupling in this aqueous solvent system. Arylboronic acids with functional groups such as alkyl, methoxy, nitro, and halogen were found to work well, resulting in the desired biaryl products (Table 1). These results indicate that **3a**–**c** are good substrates for Suzuki coupling, presumably due to the electron-withdrawing effects of the α-carbonyl group. These observations also suggest that α-ketophosphonic acid moiety can survive the Suzuki coupling conditions and offer additional support for its chemical stability.



Scheme 1. Reagents and conditions: (a) $P(OMe)_3$, 1 h; (b) TMSBr, CH_2Cl_2, overnight; (c) 1 equiv NaOH in MeOH.

Table 1. $Pd(OAc)_2$ catalyzed aqueous Suzuki coupling reaction of arylboronic acids and **3a**–**c**[a]

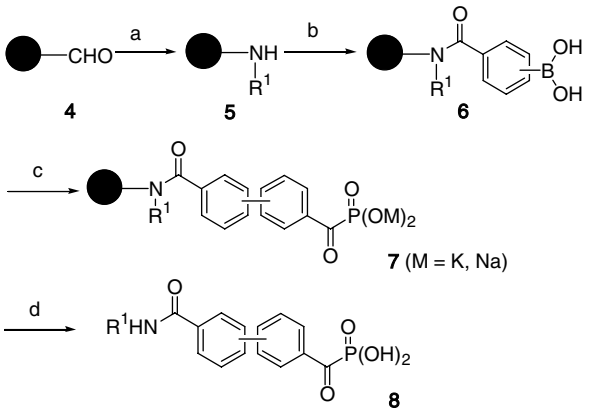
Entry	Arylboronic acid	**3a**–**c**	Result (% conv.)[b]
1	3-$MeC_6H_4B(OH)_2$	a	>95
2	3-$MeC_6H_4B(OH)_2$	b	>95
3	3-$MeC_6H_4B(OH)_2$	c	>95
4	4-$MeC_6H_4B(OH)_2$	b	>95
5	2-$MeC_6H_4B(OH)_2$	b	77
6	3-$NO_2C_6H_4B(OH)_2$	b	85
7	3-$MeOC_6H_5B(OH)_2$	b	>95
8	4-$ClC_6H_5B(OH)_2$	b	>95

[a] Reaction conditions: arylboronic acid/**3a**–**c** = 2/1, 5% $Pd(OAc)_2$, a mixed solvent of 10% aqueous K_2CO_3 and CH_3CN (2:1 v/v), microwave, 10 min.

[b] Conversion determined by HPLC.

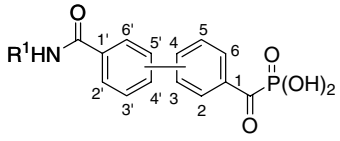
To develop solid-phase methods, we initially considered two approaches for attaching **3a**–**c** to solid support to form a polymer-bound aryl bromide and then conduct the Suzuki coupling with arylboronic acids. One was to attach **3** to the solid support through ketone carbonyl, either by reacting with a hydrazine resin to form a hydrazone linkage[19] or with a diol resin to form ketal linkage.[20] The other was to tether **3** to the resin via a phosphonate ester linkage using Mitsunobu conditions.[21] However, all these attempts failed to load **3** to resins presumably due to the poor solubility of **3** in organic solvents. Therefore, we decided to develop an alternative approach to conduct a reversed Suzuki reaction,[22] by reacting a polymer-bound aryl boronic acid with **3**.

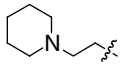
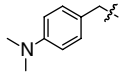
As shown in Scheme 2, ArgoPore resins (Argonaut Technologies) were used because of their compatibility with a wide range of solvents including polar protic solvents such as water that is required for the Suzuki coupling. ArgoPore Rink-NH_2 resin **5** was allowed to react with 3- or 4-carboxyphenylboronic acid to give resin-bound boronic acids **6** (R^1 = H). To introduce R^1 substituents, ArgoPore-BAL resin **4** (ArgoPore resin functionalized with a BAL linker)[23] was derivatized with primary amines by reductive amination to give resin-bound secondary amines **5**, followed by the coupling with 3- or 4-carboxyphenylboronic acid to give **6**. Aqueous Suzuki coupling of **6** with the three α-ketophosphonic acids **3a**–**c** generated the biaryl products **7**.[24] After acidic cleavage from the resin with TFA, products **8** were purified by preparative HPLC.[25] Representative examples of α-ketophosphonic acids **8a**–**l** are shown in Table 2. Compounds **8a**–**f** represent six isomeric biaryl scaffolds with different spatial orientations, and **8g**–**l** are biaryl analogues with substituents incorporated into



Scheme 2. Reagents and conditions: (a) (i) R^1NH_2, TMOF/DMF (1:1), 30 min; (ii) HOAc, MeOH, $NaBH_3CN$, overnight; (b) HO_2C–C_6H_4–$B(OH)_2$, PyBOP, DIEA, DMF, overnight; (c) **3a**–**c**, $Pd(OAc)_2$, 10% K_2CO_3 and CH_3CN (2:1 v/v), microwave, 10 min; (d) CF_3COOH/CH_2Cl_2 (1:1), 20 min.

Table 2. Solid-phase synthesis of biaryl α-ketophosphonic acids **8** using **3a**–**c** via aqueous Suzuki coupling reaction



Compds	R_1	**3a**–**c**	Attachment points	Yield[c] (%)
8a[a]	H	a	4′–4	32
8b[a]	H	b	4′–3	39
8c[a]	H	c	4′–2	49
8d[a]	H	a	3′–4	41
8e[a]	H	b	3′–3	28
8f[a]	H	c	3′–2	53
8g[b]		b	4′–3	22
8h[b]		b	4′–3	31
8i[b]		b	4′–3	34
8j[b]		b	4′–3	31
8k[b]		b	4′–3	20
8l[b]		b	4′–3	20

[a] ArgoPore Rink-NH_2 resin **5** was used with a loading of 0.60 mmol/g.
[b] ArgoPore BAL resin **4** was used with a loading 0.62 mmol/g.
[c] Isolated yields after preparative HPLC.

the amide portion of scaffold **8b**. Using the same procedure, substituents could be incorporated in scaffolds **8a** and **8c**–**f** as well.

It is also conceivable to use this solid-phase approach to incorporate additional sets of diversity by using boronic acids such as (4-carboxy-2-nitrophenyl)boronic acid and (3-carboxy-5-nitrophenyl)boronic acid. After the nitro group is reduced on support, the resulting amino group could be readily derivatized into other useful functionalities including carboxamides, sulfonamides, and ureas.

In summary, we developed a new method for the synthesis of functionalized biaryl α-ketophosphonic acids using sodium bromobenzoyl phosphonates as precursors via aqueous Suzuki coupling on solid support. To the best of our knowledge, these are the first reported examples of palladium-catalyzed syntheses of compounds incorporating α-ketophosphonic acids. This direct approach provides rapid access to a wide range of diverse biaryl α-ketophosphonic acids, which constitute an interesting class of inhibitors of protein tyrosine phosphatases.[5]

Acknowledgments

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16. Preparation of **3c**: To a stirred 2-bromobenzoyl chloride (2.61 mL, 20 mmol, neat) at 0 °C was added slowly trimethyl phosphite (2.36 mL, 20 mmol). The mixture was allowed to stir at rt for 1 h, and then treated with TMSBr (5.81 mL, 44 mmol) in 100 mL of CH_2Cl_2 for overnight. After concentrated in vacuo, NaOH (0.8 g, 20 mmol) in 80 mL of MeOH was added and the product was collected by filtration to give 4.96 g of **3c** as an off-white powder (yield 86%). ^{1}H NMR (DMSO-d_6, 300 MHz) 8.30 (d, 1H), 7.58 (d, 1H), 7.32 (m, 2H). ^{31}P NMR (DMSO-d_6, 121 MHz) −2.1. MS: $m/z = 262.9$ (M^+-1, 100%).
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24. Typical procedure for solid-phase Suzuki coupling: To a suspension of resin **6** (50 mg, ~0.6 mmol/g) in 0.6 mL of a mixed solvent of 10% K_2CO_3 and CH_3CN (v/v, 2/1) was added **3** (25 mg, 0.09 mmol), and 1.0 mg of $Pd(OAc)_2$. The reaction mixture was irradiated in a domestic 1000 W microwave oven for 10 min (at 20% power). The resin was washed with water (3 × 2 mL), DMF (3 × 2 mL), and CH_2Cl_2 (3 × 2 mL). Final products were cleaved from the resin with 50% TFA in CH_2Cl_2.
25. HPLC purification was carried out on a preparative Nucleosil C_{18} reverse phase column. The following mobile phase gradient system was used: (solvent A: water with 0.1% TFA; solvent B: acetonitrile with 0.1% TFA): 0 min, 100% A; 5 min, 100% A; 20 min, 100% B; 28 min, 100% B; 30 min, 100% A. Flow rate 12 mL/min. The yields for all the compounds were not optimized. The low yields observed are probably due to poor recovery of these highly polar compounds during HPLC purification.