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Facile synthesis of 9-(arenethenyl)purines via Heck reaction of 9-vinylpurines and aryl halides

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Abstract—The first example of a Heck reaction with 9-vinylpurines and aryl halides is described. It gives exclusively *E*-9-(arenethenyl)purines in high yields. Subsequent hydrogenation furnishes 9-(arenethyl)purines quantitatively.

In one of our kinase inhibitor drug discovery programs we required ready access to *E*-9-(arenethenyl)purines **1**, particularly those bearing further substitution on the terminal phenyl group. Literature methods for the preparation of **1** are based on the Horner–Wadsworth–Emmons (HWE) reaction of N^9-phosphorylmethylpurine and benzaldehydes.[1,2] In addition to limited availability of functionalized benzaldehydes, this transformation usually yields a mixture of *Z*- and *E*-isomers, which can result in separation difficulties in some cases. Moreover, the preparation of necessary HWE reagents is not trivial and the strongly basic conditions are often incompatible with many functional groups. Very recently, a single example of a copper-mediated coupling of an alkenyl boronic acid with 9*H*-purine was reported to provide the alkenylation product in high yield.[3] The difficulty in extending this methodology more broadly in the synthesis of **1** is that several synthetic steps are required for the preparation of suitably functionalized alkenyl boronic acids. We envisaged that a Heck reaction of 9-vinylpurine and aryl halides could be an efficient way of making **1** considering the excellent functional group compatibility in this reaction and abundant availability of various poly-functionalized aryl halides (Table 1). To our knowledge, Heck reactions of 9-vinylpurines have not been reported.

The preparation of 9-vinylpurines is well documented in the literature.[4] Thus, commercially available 6-chloro and 2,6-dichloropurine were easily converted to their corresponding N^9-vinyl derivatives **2a** and **2e** by reacting both with excessive vinyl acetate in the presence of catalytic amounts of H_2SO_4 and $Hg(OAc)_2$. Subsequent displacement of the chloride at C-6 in **2a** or **2e** by methylamine, cyclopropylamine, or (4-dimethylphosphonyl)aniline gave **2b–d**, **f**, respectively. All aromatic halides **3** used in our studies were commercially available except **3a** and **3d**, which were prepared by coupling the requisite acids and amines.

We began our investigations by reacting **2b** and **3b** at 100 °C in DMF utilizing $Pd(OAc)_2/P(o\text{-tol})_3$ as the catalyst system and $(i\text{-Pr})_2NEt$ as the base. The reaction proceeded smoothly despite the steric hindrance of **3b**, giving the desired product **1b** in high yield and exclusively as the *E* geometrical isomer. The regioisomer resulting from arylation at α position, a product reported in similar Heck reactions of vinyl ethers or *N*-vinyl amides/imides,[5] was not observed. Encouraged by these preliminary results we expanded the scope of our investigations to other substrates **2** and **3**. As outlined in Table 1, good to excellent yields were obtained from all reactions, which were not optimized. Most reactions proceeded to completion after heating at 100 °C for 15 h, and in each case, crude HPLC traces indicated conversion to a single product that was determined to result from β-attack and be exclusively the *E*-isomer. Both aromatic iodides and bromides were suitable

Keywords: 9-Vinylpurine; Heck reaction; 9-(Arenethenyl)purine; 9-(Arenethyl)purine.
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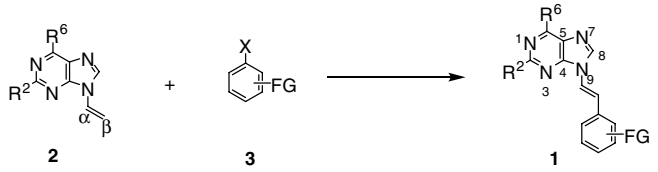
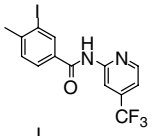
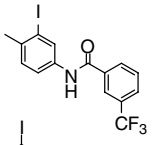
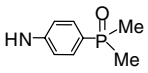
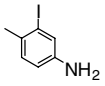
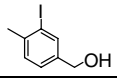
Table 1. Heck reaction of *N*-vinylpurines **2** and aryl halides **3**



2 **3** **1**

2		3		1	Yield (%)
R^2 H	R^6 Cl	**2a**		**3a**	**1a**	81[a]
H	NHMe	**2b**		**3b**	**1b**	86[b]
				**3c**	**1c**	58[b]
				**3d**	**1d**	82[b]
H		**2c**		**3e**	**1e**	66[b]
				3a	**1f**	88[b]
H		**2d**		**3f**	**1g**	62[b]
				**3g**	**1h**	74[b]
Cl	Cl	**2e**		**3h**	**1i**	78[c]
Cl		**2f**		**3b**	**1j**	70[d]

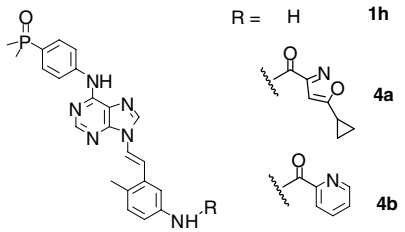
[a] 5 mol % $Pd[P(t\text{-}Bu)_3]_2$, 120 mol % $(i\text{-}Pr)_2NEt$, DMF, 100 °C, 5 h.
[b] 2.5 mol % $Pd(OAc)_2$, 5 mol % $P(o\text{-}tol)_3$, 120 mol % $(i\text{-}Pr)_2NEt$, DMF, 100 °C, 15 h.
[c] 5 mol % $Pd[P(t\text{-}Bu)_3]_2$, 120 mol % $(i\text{-}Pr)_2NEt$, DMF, microwave, 150 °C, 20 min.
[d] 15 mol % $Pd(OAc)_2$, 30 mol % $P(o\text{-}tol)_3$, 360 mol % $(i\text{-}Pr)_2NEt$, DMF, microwave, 90 °C, 10 min.

coupling partners. Most reactions were run with conventional heating but microwave-assisted reactions worked equally well.

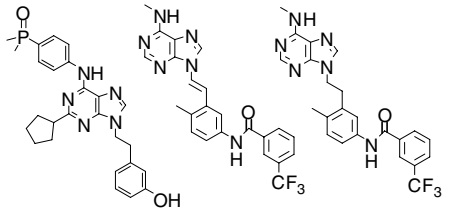
Heck reactions of **2a**, **e** and **f** were of particular interest since Cl substitution by S_NAr and/or palladium-mediated cross-coupling reactions offer the potential for further elaboration at either C-2 and/or C-6 on the purine template.[6] Gratifyingly, the reaction of **2f** and **3b** furnished **1j** in high yield, suggesting that the Cl at C-2 did not interfere with the Heck reaction. To the contrary, the reaction of **2a** and **3a** yielded complex mixtures under general reaction conditions, presumably resulting from interfering chemistry at C-6 despite the increased reactivity of aromatic iodides relative to chlorides in these reactions. This result is consistent with the increased reactivity at C-6 relative to C-2 on the purine template in mechanistically relevant metal-catalyzed cross-coupling reactions of the corresponding chlorides.[6a] Several alternate conditions consisting of different Pd, ligand and base combinations gave low conversions and/or complex mixtures.[7] However, further screening led to the identification of a very efficient catalyst for this reaction, $Pd[P(t\text{-}Bu)_3]_2$,[8] which furnished **1a** in high yield. This catalyst was also successfully applied to the reaction of **2e** and **3h**, where the Cl at C-2 was again found to be benign.

As expected, many functional groups, which would be incompatible with standard HWE conditions, including NH_2, alcoholic OH, phenolic OH, indolyl NH, amide NH, and aldehydes, were tolerated in this reaction. The presence of these functional groups and their incorporation without the need for protection highlights the synthetic utility of this reaction as further derivatization to more complex purines was often desired. For example, **1h** was coupled with 5-cyclopropylisoxazole-3-carboxylic acid or 2-picolinic acid under standard amide

bond formation condition (EDCI/HOBt), furnishing amides **4a** and **4b** in high yields, respectively.



Since several N^9-(arenethyl)purine compounds have been reported as potent dual Src/Abl kinase inhibitors[9] (e.g., AP23464 has an $IC_{50} < 1$ nM against Src kinase), we were also interested in converting the Heck coupling product **1** to its saturated analog. As such, **1d** was smoothly hydrogenated to **5** using standard conditions (H_2, Pd/C, EtOAc). Despite a 2-step procedure, this Heck-hydrogenation route to N^9-(arenethyl)purines still offers significant advantages over the existing methods for the following considerations: (i) de novo construction of N^9-substituted purines requires early incorporation of N-9 substituents in a lengthy reaction sequence,[10] (ii) S_N2 alkylation of 9*H*-purine with (2-haloethyl)arenes is often accompanied with significant β-elimination[11] and the pool of commercially available (2-haloethyl)arenes is very limited, (iii) Mitsunobu reactions of 9*H*-purine with alcohols suffer from tedious preparation of (2-hydroxyethyl)arenes and poor yields due to β-elimination,[12] (iv) functional group compatibilities of these existing methods are generally poor.



To access N^9-(arenethyl)purine directly from **2**, a reductive Heck coupling of **2b** and iodobenzene in the presence of HCO_2H was attempted.[13] Unfortunately, this reaction did not yield the desired hydroarylation product but generated a small amount of Heck product **1**, with the major product being 6-(methylamino)-9-ethylpurine. This result suggests that the insertion of ArPdX complex into N^9-vinyl of **2** is slow and that the reduction of 9-vinylpurine by HCO_2H itself predominates, yielding 9-ethylpurine in a manner similar to the reduction of an enamine in the Leuchart–Wallach reaction.[14]

In summary, we have demonstrated that 9-vinylpurines undergo Heck reactions cleanly and efficiently with a variety of substituted aryl halides.[15] Through this reaction, a number of highly potent, purine-based dual Src/Abl kinase inhibitors bearing 9-(arenethenyl) substituents were prepared.[16] Subsequent hydrogenation of the Heck reaction products gave rapid access to 9-(arenethyl)purines. Importantly, the use of aryl halides as opposed to substituted benzaldehydes (HWE reaction) substantially increased the pool of diverse starting materials and provided access to a number of products bearing reactive functionalities without the need for protection/de-protection strategies.

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7. Catalysts investigated: 2.5 mol % $Pd_2(dba)_3$/5 mol % $Pd[P(t\text{-}Bu)_3]_2$, 5 mol % $Pd_2(dba)_3$/10 mol % $P(o\text{-}tol)_3$.
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15. *General procedure*: a solution of **2c** (1.01 g, 5 mmol), **3a** (2.23 g, 5.5 mmol), $Pd(OAc)_2$ (28 mg, 0.125 mmol), P(*o*-tol)$_3$ (76 mg, 0.25 mmol) in DMF (10 mL) was degassed by bubbling N_2 for 10 min. (*i*-Pr)$_2$NEt (2.60 mL, 15 mmol) was added under N_2. The resulting solution was stirred at 100 °C for 15 h. Water was added and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated on a rotavap, and then subjected to silica gel column chromatography (5% MeOH/CH_2Cl_2), yielding 2.19 g of the desired product **1f** as a white solid, mp 232 °C. MS $[M+H]^+$ 480; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.44 (s, 1H), 8.72 (s, 1H), 8.69 (s, 1H), 8.59 (s, 1H), 8.38 (m, 2H), 8.05 (m, 1H), 8.03 (d, 1H, $J = 14.7$ Hz), 7.87 (d, 1H, $J = 7.9$ Hz), 7.81 (d, 1H, $J = 14.7$ Hz), 7.55 (d, 1H, $J = 4.1$ Hz), 7.42 (d, 1H, $J = 8.0$ Hz), 3.09 (m, 1H), 2.43 (s, 3H), 0.74 (m, 2H), 0.66 (m, 2H).
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