Efficient Pd-Catalyzed Coupling of Tautomerizable Heterocycles with Terminal Alkynes via C-OH Bond Activation Using PyBrOP

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Efficient Pd-Catalyzed Coupling of Tautomerizable Heterocycles with Terminal Alkynes via C-OH Bond Activation Using PyBrOP

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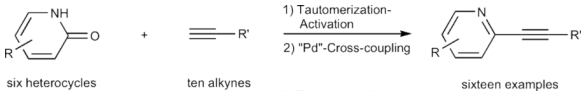
Abstract



The direct alkynylation of tautomerizable heterocylcles is described via a two-step process involving in situ C-OH activation with bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP) followed by Sonogashira coupling with a wide range of alkyl or aryl terminal alkynes using a copper free system employing $PdCl_2(CH_3CN)_2$ and 2-(dicyclohexylphosphino)biphenyl.

The Sonogashira coupling reaction[1] of (hetero)aryl-, and vinyl halides with terminal alkynes is the most straightforward and efficient method to construct (hetero)arylalkynes, and enynes, [2] which are important substructures in organic materials,3 natural products, and medicinal agents.4 With regard to heteroaryl halides, the corresponding iodides, bromides and even chlorides have been successfully employed. However, the less reactive heteroaryl bromides and -chlorides, typically require elevated temperatures with bulky phosphine ligands.5

Heteroaryl halides are conventionally derived from heteroarenes or heteroarenols, which are more readily available. The conversion of these precursors to the required heteroaryl halides can be costly and often requires toxic reagents or multiple-step syntheses.[6] Therefore, direct C-H or C-OH activation of heteroarene compounds for cross-coupling processes are greatly desired.[7]

Recently Kang and co-workers reported the Pd-catalyzed cross-coupling reactions of tautomerizable heterocycles with aryl boronic acids via C-OH bond activation using phophonium salts as activating reagents.7e This new protocol demonstrated excellent reactivity and chemoselectivity, which makes it an attractive route for direct arylation of tautomerizable heterocycles. With our long-standing interests in synthesis and diversification of heterocycles, especially in the field of nucleoside chemistry,[10] we became very interested in applying the C-OH activation strategy into other types of cross-coupling reactions. Herein, we report our studies of the Sonogashira-type reactions of tautomerizable heterocycles activated by bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP) with terminal alkynes (Scheme 1).

Considering the diversity of tautomerizable heterocycles and terminal alkynes, we initially explored a range of conditions for direct alkynylation of the model substrate 2-quinoxalinone

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Supporting Information Available: Experimental procedures and characterization as well as NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

with 1-octyne. 2-Quinoxalinone was first activated *in situ* with PyBrOP (1.2 equiv) and triethylamine (3 equiv) in 1,4-dioxane at room temperature for 2 hours. Several cross-coupling conditions developed for Sonogashira coupling reactions were explored. The cross-coupling was conveniently monitored by electrospray mass spectrometry with the dissaperance of the active alkoxyphosphonium salt at *m/z* 386.2 and concomittant formation of the cross-coupling product at *m/z* 239.3 $[M + H]^+$. The classic Sonogashira coupling conditions employing catalytic $PdCl_2(PPh_3)_2$ and CuI (**condition A**) furnished the desired cross-coupling product in 91% yield in 4 hours at room temperature (Table 1). The $PdCl_2(CH_3CN)_2$/P*t*Bu_3/CuI catalytic system in **conditions B** and **-C** developed by Buchwald for Sonogashira coupling of aryl bromides led to only homocoupling of the alkynes.[5a] Under **condition D**, a copper-free system employing $PdCl_2(CH_3CN)_2$ and 2-(dicyclohexylphosphino)biphenyl at 85 °C utilized for less reactive aryl chlorides,[5c] the cross-coupling proceeded smoothly with an 87% isolated yield. Addition of CuI to **condition D** provided **condition E**.[5c] Unfortunately, only homocoupling of the alkyne was observed with **condition E**.

Next we investigated the substrate scope using the optimal **conditions A** and **-D**. An array of tautomerizable heterocycles were reacted with various terminal alkynes under both conditions, and the results are reported in Tables 2 and 3. Under **condition A**, quinoxalinone **1** and benzothiazolinone **2** successfully cross-coupled with a wide variety of aryl- and alkyl-acetylenes to afford **1a**–**1f** and **2d** in yields ranging from 63–93% (Table 2). **Condition A** also showed excellent functional group tolerance (−OH, $-NO_2$, $-NH_2$, −TMS), and undesirable etherification or amination were not observed in **1c** and **1e** (Table 2). However, the classic Sonogashira conditions failed for substrates **3**–**6** (Table 3) providing no observed cross-coupled products. Additionally, **condition A** failed for coupling of **1** with 2-ethynylpyridine. For these cases, the Buchwald catalyst system in **condition D** was investigated.

The highly functionalized pyrazolo[3,4-*b*]pyridine **3** smoothly coupled under **condition D** with phenylacetylene and triethylsilylacetylene to provide **3d** and **3h** in 87% and 77% yields respectively (Table 3). Importantly, other methods to activate the carboxamide function of **3** including chlorination and triflation were unsuccessful due to the presence of the basic pyridine moieties serving to highlight the utility of the PyBroP mediated activation. Coupling of thieno[3,2-*d*]pyrimidin-4-one **4** and pyrimidin-2(1*H*)-one **5** employing **condition D** with phenylacetylene, *tert*-butylacetylene, and 1-cyclohexenylacetylene provided **4d**, **4i**, **5d**, and **5j** in yields ranging from 76–91% demonstrating the generality of **Condition D**.

6-Alkynylpurine ribonucleosides have attracted attention due to their potent cytostatic activity.[11] Conventionally, these have been prepared from protected inosines, which must be first converted to 6-iodo-purine derivatives to obtain sufficient reactivity to participate in cross-coupling with alkynes.[6b] However, using PyBroP activation and **condition D**, cross-coupling of protected inosine derivative **6** with phenylacetylene and triethylsilylacetylene provided **6d** and **6h** in 78% and 61% yields respectively (Table 3).

As reported by Buchwald,[5c] we confirmed the trimethylsilyl (TMS) group was not compatible under **condition D**, as significant desilylation of the products were observed. Instead, triethylsilylacetylene was used to afford the more stable TES-protected products (**3h** and **6h**, Table 3). **Condition D** suffered from lower functional group tolerance as 6-nitro benzothiazolinone **2** failed to couple due to reduction of the nitro group and **condition D** also required protection of the ribofuranosyl hydroxyl groups in **6** to prevent Pd-catalyzed etherification. For both **conditions A** and **−D**, we observed that slow addition of the alkyne was required to ensure complete conversion of substrates, when using electron-rich arylacetylene (**1f**, Table 2) or electron-deficient heterocycles (**3** and **6**, Table 3). Overall, **condition A** is recommended due to its greater functional group tolerance and practicality since

this is performed at room temperature; however, **condition D**, which requires elevated temperatures, is more versatile and allows coupling of a wider range of heterocyclic substrates.

We propose the following mechanism for the copper-free direct alkynylation of tautomerizable heterocycles, based on the studies by Soheili[9] (Scheme 2). The tautomerizable heterocycle is first activated by PyBrOP in the presence of triethylamine to afford the phosphonium salt **I**. Once the active Pd(0) species is formed, the catalytic cycle begins with the oxidative addition of the phosphonium salt **I** to generate Pd(II) complex **II**. Next, ligand dissociation followed by alkyne complexation leads to Pd(II) complex **III**. Deprotonation of the alkyne by Cs_2CO_3 and ligand exchange provides Pd(II) acetylide complex **IV**, which undergos reductive elimination to afford the cross-coupling product and regenerate the Pd(0) species.

In conclusion, we have developed an efficient Pd-catalyzed system for direct alkynylation of tautomerizable heterocycles via C-OH bond activation using PyBrOP. The protocols showed great versatility and efficiency, enabling cross-couplings between a variety of tautomerizable heterocycles and terminal alkynes with diverse electronic and steric features. The mechanism of the direct Cu-free cross-coupling is proposed to proceed through a stepwise process of C-OH activation using PyBrOP, followed by Cu-free Sonogashira type catalytic cycle.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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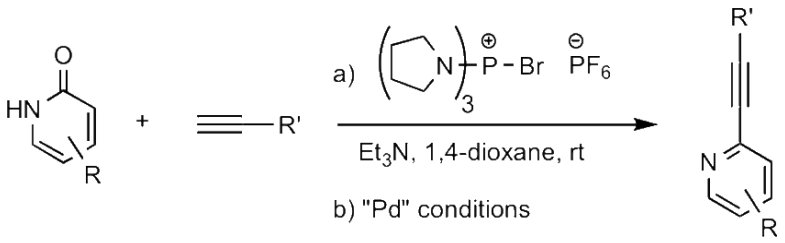
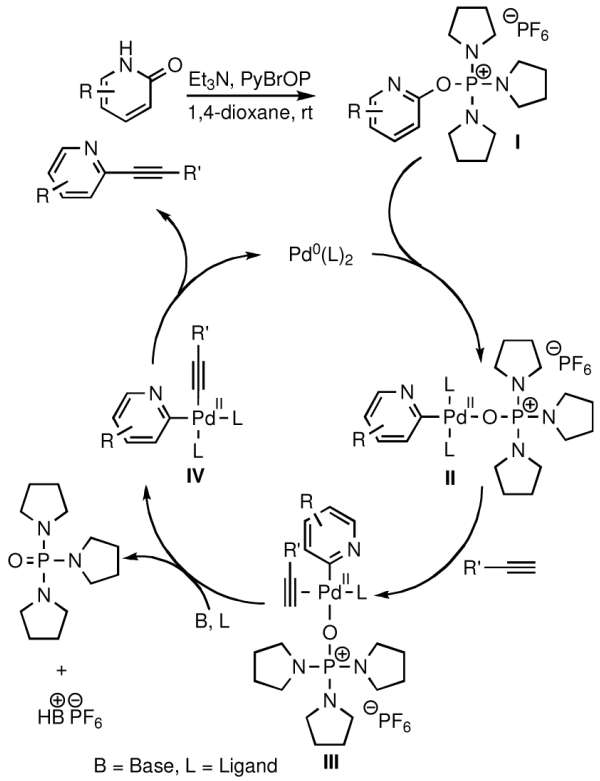


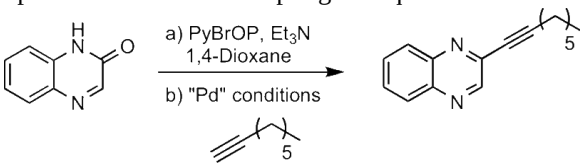
Scheme 1.
Pd-catalyzed Sonogashira reaction of tautomerizable heterocylces



Scheme 2.
Proposed mechanism of copper-free Sonogashira coupling of tautomerizable heterocycles

Table 1

optimization of cross-coupling of 2-quinoxalinone with 1-octyne[a]



"Pd" conditions	conv (%)[b]	yield(%)[c]
condition A[d]: $PdCl_2(PPh_3)_2$,CuI, rt	100	91
condition B[d,e]: $PdCl_2(CH_3CN)_2$ *t*-Bu_3P, CuI, rt	<10	/
condition C[d,e]: $PdCl_2(CH_3CN)_2$ *t*-Bu_3P, CuI, 65 °C	<10	/
condition D[e,f]: $PdCl_2(CH_3CN)_2$/P*, Cs_2CO_3, 85 °C	100	87
condition E[e,f]: $PdCl_2(CH_3CN)_2$/P*, CuI, Cs_2CO_3, 85 °C	<10	/

[a] General conditions: 2-quinoxalinone (0.5 mmol), PyBrOP (1.2 equiv) and Et_3N (3 equiv) in 1,4-dioxane (4 mL) at rt for 2 h; then, Pd catalyst (5 mol %), 1-octyne (1.5 equiv), with or without CuI (5 mol %), with or without Cs_2CO_3 (2.5 equiv) at indicated temperature for 4 h;

[b] Monitored by LC-MS and ^1H NMR;

[c] Isolated yields;

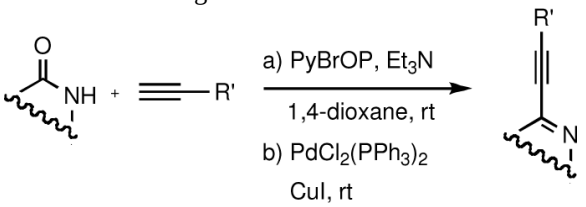
[d] 6 equivalents of Et_3N were used;

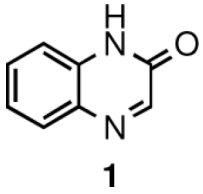
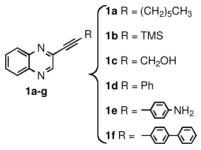
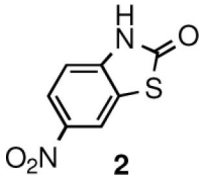
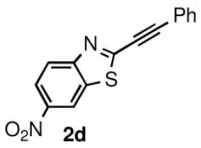
[e] Pd:P= 1:3;

[f] P* = 2-(Dicyclohexylphosphino)biphenyl.

Table 2

substrate screening under **condition A**.[a]



substrate	product	time (h)[b]	yield(%)[c]
 **1**	 **1a-g** **1a** R = $(CH_2)_5CH_3$ **1b** R = TMS **1c** R = CH_2OH **1d** R = Ph **1e** R = NH_2 **1f** R =	4	91
		6	83
		6	75
		3	93
		4	74
		4	78[d]
 **2**	 **2d**	6	63

[a]General conditions: substrates (0.5 mmol), PyBrOP (1.2 equiv) and Et_3N (6 equiv) in 1,4-dioxane (4 mL) at rt for 2 h, followed by **condition A**: $PdCl_2(PPh_3)_2$ (5 mol %), CuI (5 mol %), alkyne (1.5 equiv), at rt until mass spectra shows no activated substrates;

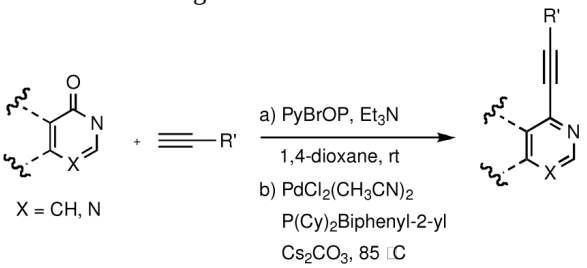
[b]Determined by LC-MS and ^1H NMR;

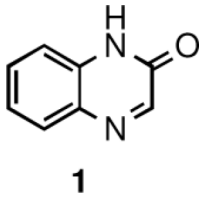
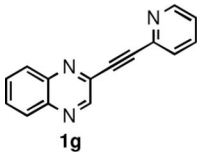
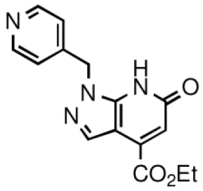
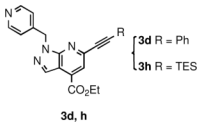
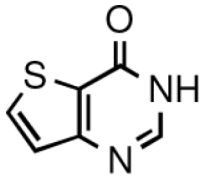
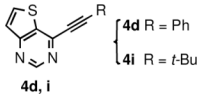
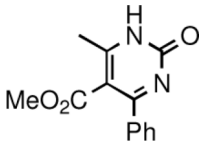
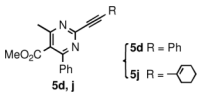
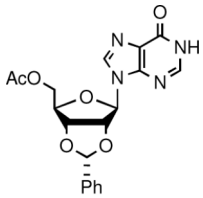
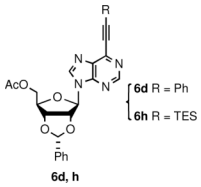
[c]Isolated yields;

[d]A solution of alkyne in 1.5 mL 1,4-dioxane was injected into the reaction vessel over 1.5 h via syringe pump.

Table 3

substrate screening under **condition D**.[a]



substrate	product	time (h)[b]	yield(%)[c]
 1	 1g	4	77
 3	 3d, h	6	87[d]
		6	77[d]
 4	 4d, i	3	85
		3	82
 5	 5d, j	4	91
		4	76
 6	 6d, h	6	78[d]
		6	61[d]

[a]General conditions: substrates (0.5 mmol), PyBrOP (1.2 equiv) and Et3N (3 equiv) in 1,4-dioxane (4 mL) at rt for 2 h, followed by **condition D**: PdCl2(CH3CN)2 (5 mol %), 2-(dicyclohexylphosphino)biphenyl (15 mol %), and Cs2CO3 (2.5 equiv) were pre-incubated with the activated substrates at rt for 25 min at 85 °C, followed by addition of alkynes;

[b] Determined by LC-MS and ^{1}H NMR;

[c] Isolated yields;

[d] A solution of alkyne in 1,4-dioxane (1.5 mL) was injected into the reaction vessel over 1.5 h via syringe pump.