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Microwave Assisted Tandem Heck–Sonogashira Reactions of *N,N*-Di-Boc-Protected 6-Amino-5-iodo-2-methyl Pyrimidin-4-ol in An Efficient Approach to Functionalized Pyrido[2,3-*d*]Pyrimidines

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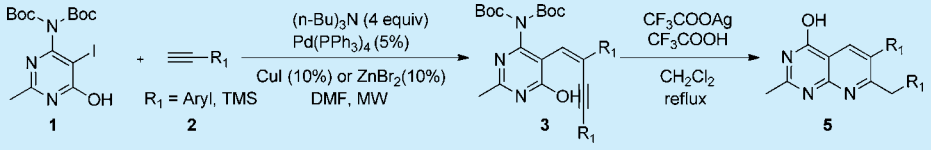
Supporting Information



ABSTRACT: A microwave assisted tandem Heck–Sonogashira cross-coupling reaction between 6-*N,N*-di-Boc-amino-5-iodo-2-methyl pyrimidin-4-ol and various aryl alkynyl substrates has been developed. This process generates novel 5-enynyl substituted pyrimidines, which can be transformed to novel functionalized pyrido[2,3-*d*]pyrimidines by way of a silver catalyzed cyclization reaction.

Pyrido[2,3-*d*]pyrimidine is a core structure that is found in a large variety of substances that exhibit important biological activities. For example, this heterocyclic structural motif is present in AZD8055 (A), a selective ATP-competitive PI3K-Akt-mTOR signaling pathway inhibitor used for the treatment of antitumor,[1] piritrexim (B), a lipid-soluble inhibitor of dihydrofolate reductase (DHFR) that displays high potency for the treatment of metastatic urothelial cancer,[2] and pyrido[2,3-*d*]pyrimidine derivative C that is a hepatitis C virus replicon inhibitor[3] (Figure 1). Also, substances that possess the pyrido[2,3-*d*]pyrimidine framework have other interesting biological properties such as anticardiovascular,[4] anti-inflammatory,[5] antibacterial,[6,7] and anti-Parkinson's activities.[8] The few methods thus far devised to prepare these substances involve condensation reactions of pyridine or pyrimidine[9] (Scheme 1), which are only applied with difficulty when diversified substitution patterns are required. Herein, we describe a novel palladium catalyzed microwave-assisted tandem Heck–Sonogashira reaction of 6-*N,N*-di-Boc-amino-5-iodo-2-methylpyrimidin-4-ol with terminal alkynes (HC≡CR, R = aryl group or TMS) that forms functionalized enyne (−C═C−C≡C−) substituted pyrimidines, which then undergo cyclization to generate novel diverse substituted pyrido[2,3-*d*]pyrimidines in good to excellent yields.

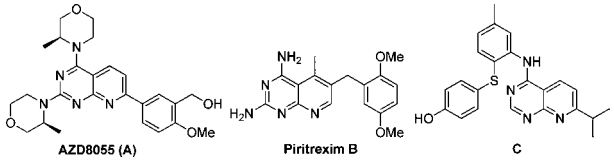
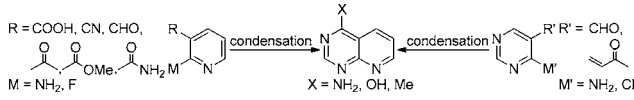
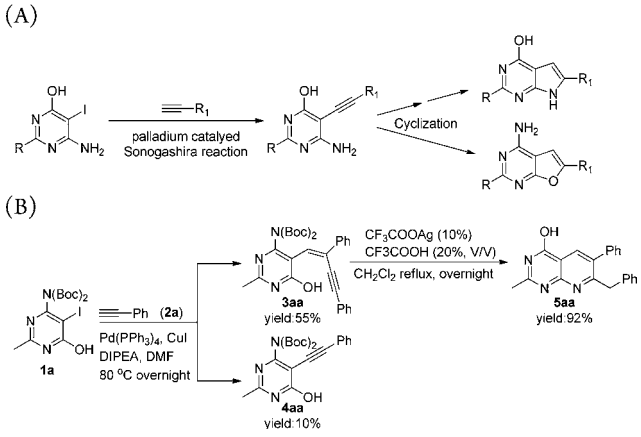


Figure 1. Representative bioactive pyrido[2,3-*d*]pyrimidines.

Scheme 1. Common Methods To Prepare Pyrido[2,3-*d*]pyrimidines



Scheme 2. Palladium Catalyzed Cross-Coupling of 2-Substituted-6-amino-5-iodopyrimidin-4-ols

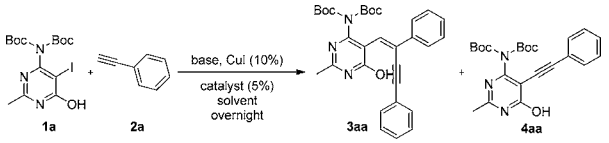


Palladium catalyzed Sonogashira reactions of 2-substituted-6-amino-5-iodopyrimidin-4-ols (Scheme 2A) have been previously applied to the synthesis of functionalized heterocyclic pyrimidines.[10] However, the poor solubilities of 2-substituted-

Received: May 22, 2014
Published: June 23, 2014

dx.doi.org/10.1021/ol501459e | *Org. Lett.* 2014, 16, 3524–3527

Table 1. Optimization of Reaction Conditions for the Formation of 5-Enynyl Substituted Pyrimidine 3aa[a]



				yield (%)[d]	
entry	temp	Pd-catalyst	base; solvent	3aa	4aa
1	80 °C	$Pd(PPh_3)_4$	DIPEA; MeCN	38	20
2	80 °C	$Pd(PPh_3)_4$	DIPEA; toluene	53	17
3	80 °C	$Pd(PPh_3)_4$	DIPEA; DMF	55	10
4	80 °C	$Pd(PPh_3)_4$	DIPEA; THF	43	15
5	80 °C	$Pd(PPh_3)_4$	Et_3N; DMF	40	18
6	80 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	67	5
7	80 °C	$Pd(PPh_3)_4$	DABCO; DMF	20	40
8	80 °C	$Pd(PPh_3)_4$	DBU; DMF	<5	45
9	80 °C	$PdCl_2(PPh_3)_2$	$(n\text{-}Bu)_3N$; DMF	40	32
10	80 °C	$Pd(OAc)_2$, PPh_3	$(n\text{-}Bu)_3N$; DMF	trace	
11	80 °C	Pd/C, PPh_3	$(n\text{-}Bu)_3N$; DMF	NR	
12	80 °C	$Pd_2(dba)_3$, PPh_3	$(n\text{-}Bu)_3N$; DMF	NR	
13	60 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	52	21
14	70 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	59	8
15	90 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	57	4
16	100 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	47	6
17[b]	80 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	NR	
18[c]	80 °C	$Pd(PPh_3)_4$	$(n\text{-}Bu)_3N$; DMF	71	<5

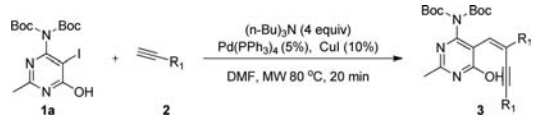
[a]Unless otherwise noted, reactions were carried out under standard conditions. [b]The reactions were carried out without CuI. [c]MW, 20 min. [d]Yield of isolated product based on **1a**.

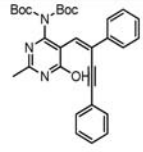
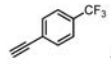
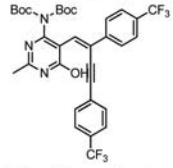
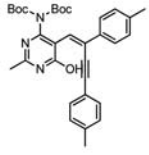
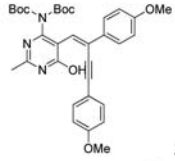
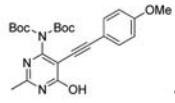
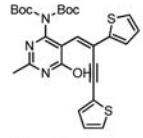
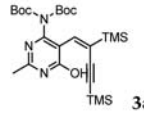
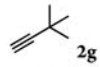
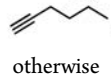
6-amino-5-iodopyrimidin-4-ols limit applications of this approach. By taking into account the fact that the solubilities of these substrates can be improved by introducing *N,N*-di-Boc amine protecting groups, we have explored the use of the protected aminopyrimidinol **1a** in palladium catalyzed Sonogashira cross-coupling reactions (Scheme 2B). Surprisingly, we observed that 6-*N,N*-di-Boc-amino-5-iodo-2-methyl pyrimidin-4-ol (**1a**) with ethynylbenzene **2a** undergoes tandem Heck−Sonogashira cross-coupling to form the unexpected and novel 5-enynyl substituted pyrimidine **3aa** as the major product (55%). In contrast, the expected Sonogashira cross-coupling product **4aa** is generated in this process in only a 10% yield. We also found that catalytic silver trifluoroacetate in trifluoroacetic acid promotes cyclization of **3aa** to form the novel pyrido[2,3-*d*]pyrimidine **5aa** in high yield.

The tandem Heck−Sonogashira reaction of terminal alkynes has been rarely described as a side reaction in the past.[11] Only few successful examples of this process, in which (thio)flavone, thiophene, naphthalene, and benzene rings react with a limited number of alkynes, have been reported.[12]

In the first phase of this effort, we examined the reaction of **1a** with ethynylbenzene **2a** using different conditions. The results show that, among a variety of different solvents such as acetonitrile, toluene, DMF, and THF (Table 1, entries 1−4), DMF is superior for this reaction. In addition, an exploration of different bases such as Et_3N, $(n\text{-}Bu)_3N$, DABCO, and DBU (Table 1, entries 5−8) uncovered the observation that the weak organic base $(n\text{-}Bu)_3N$ is more suitable for generation of enyne **3aa** while the reaction using the strong organic base DBU forms **4aa** preferentially. Among the different catalysts explored (Table 1, entries 9−12), the commonly used palladium catalyst

Table 2. Tandem Cross-Coupling Reactions of 1a with Various Alkynes 2[a]



entry	substrate	product	yield[b]
1	 **2a**	 **3aa**	71%
2	 **2b**	 **3ab**	58%
3	 **2c**	 **3ac**	60%
4	 **2d**	 **3ad**	30%
		 **4ad**	33%
5	 **2e**	 **3ae**	43%
6	 **2f**	 **3af**	73%
7	 **2g**	trace	
8	 **2h**	trace	

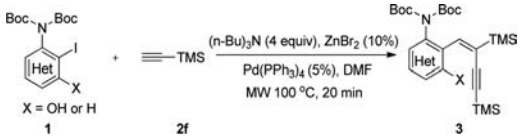
[a]Unless otherwise noted, reactions were carried out under the optimized conditions. [b]Yields of isolated product based on **1a**.

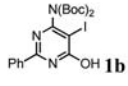
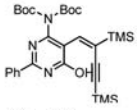
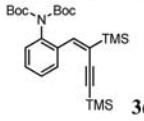
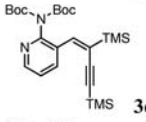
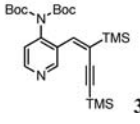
$Pd(PPh_3)_4$ is ideal and the reaction does not occur in the absence of CuI as a cocatalyst (Table 1, entry17). Finally, in the temperature range 60−100 °C (Table 1, entries 13−16), 80 °C is more suitable for this process. Finally, when the reaction is carried out under microwave irradiation at 80 °C for 20 min (Table 1, entry 18) instead of oil-heating overnight, **3aa** is generated efficiently (71%) and highly selectively. In summary, optimized conditions involve reaction in DMF at 80 °C for 20 min in the presence of 2.5 equiv of terminal alkyne, 4 equiv of $(n\text{-}Bu)_3N$, 0.05 equiv of $Pd(PPh_3)_4$, and 0.1 equiv of CuI under microwave irradiation.

To explore the alkyne substrate scope of the tandem Heck−Sonogashira process, various terminal alkynes **2** were reacted with **1a** using the optimized reaction conditions to generate 5-

dx.doi.org/10.1021/ol501459e | *Org. Lett.* 2014, 16, 3524−3527

Table 3. Tandem Cross-Coupling Reactions of 2f with *o*-Iodo-*N,N*-di-Boc Aminoarenes 1[a]



entry	substrate	product	yield[b]
1	 **1b**	 **3bf**	63%
2	 **1c**	 **3cf**	65%
3	 **1d**	 **3df**	62%
4	 **1e**	 **3ef**	59%

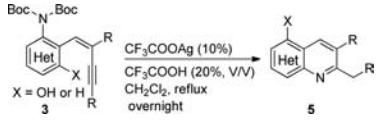
[a]Unless otherwise noted, reactions were carried out under standard conditions. [b]Yield of isolated product based on **1**.

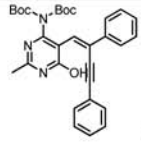
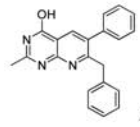
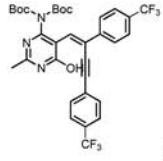
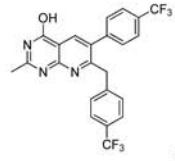
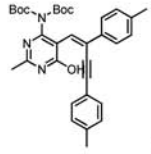
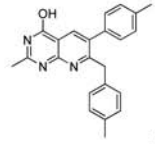
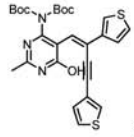
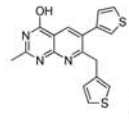
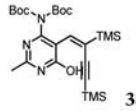
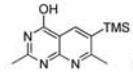
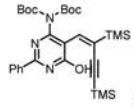
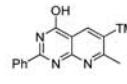
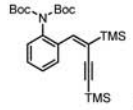
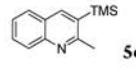
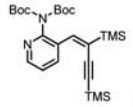
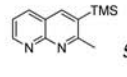
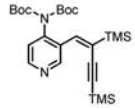
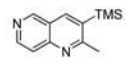
enynyl substituted pyrimidines **3** (Table 2). The results show that alkynes containing electron-withdrawing and weak electron-donating *para*-substituents on the aromatic ring react to form enyne products in modest yields (Table 2, entries 2 and 3). However, in the reaction with the *p*-methoxyphenyl alkyne **2d** was selective in that it produced **3ad** along with the normal Sonogashira coupling product **4ad** (Table 2, entry 4). Additionally, when the alkyne substituent is 2-thiophenyl (Table 2, entry 5) and trimethylsilyl (Table 2, entry 6), tandem processes occur to generate the respective enyne products **3ae** and **3af** in moderate to high yields. However, when the alkyne substrate possesses an alkyl substituent such as the *tert*-butyl or *n*-butyl group, the reaction is complicated by the production of a number of products, including those formed by double-Heck and Sonogashira reactions (Table 2, entries 7 and 8).

In a brief effort designed to probe the aryl iodide substrate range of the tandem coupling process, alkyne **2f** was reacted with other *o-iodo N,N*-di-Boc-aminoarenes. The results displayed in Table 3 show that tandem reactions of the 2-phenyl-6-*N,N*-di-Bocamino-5-iodo-pyrimidin-4-ol **1b**, protected-aminoiodobenzene **1c**, and pyridines **1d**−**e**, using $ZnBr_2$[13] in place of CuI as the cocatalyst and a higher temperature of 100 °C, led to high yielding production of the desired enyne products (Table 3, entries 1−4).

In order to demonstrate the importance of the novel tandem Heck−Sonogashira coupling process, we have explored cyclization reactions of the eneyne products promoted by catalytic silver trifluoroacetate in trifluoroacetic acid. Nearly all of the 5-enynyl substituted pyrimidines **3** and related benzene and pyridines are efficiently transformed to the novel substituted pyrido[2,3-*d*]pyrimidines **5** (Table 4 entries 1−9). Surprisingly, treatment of **3ad** under these conditions leads to production of a complicated mixture of products. Interestingly, under the cyclization reaction conditions desilylation takes

Table 4. Synthesis of Novel Functionalized Pyrido[2,3-*d*]pyrimidines[a]



entry	substrate	product	yield[b]
1	 **3aa**	 **5aa**	92%
2	 **3ab**	 **5ab**	77%
3	 **3ac**	 **5ac**	92%
4	 **3ae**	 **5ae**	93%
5	 **3af**	 **5af**	95%
6	 **3bf**	 **5bf**	91%
7	 **3cf**	 **5cf**	89%
8	 **3df**	 **5df**	82%
9	 **3ef**	 **5ef**	80%

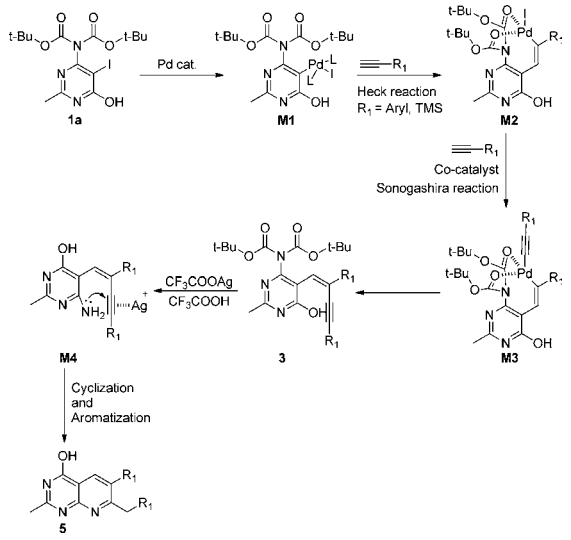
[a]Unless otherwise noted, the reactions were carried out under standard conditions. [b]Yields of isolated products based on **3**.

place at the terminal alkyne position, leading to generation of 2-methyl-3-trimethylsilyl-pyridine-fused aromatic products (Table 4, entries 5−9).

It is noteworthy that Boc protecting groups play an important role in guiding the operation of the tandem Heck−Sonogashira process. In the mechanistic route followed in this reaction, arylpalladium species **M1** is likely the first intermediate generated by the oxidative addition of Pd (0) species with the 5-iodo pyrimidine (Scheme 3). **M1** undergoes syn addition to the triple bond of the alkyne to provide the crucial Pd−C σ-bonded vinylpalladium species **M2**, which

dx.doi.org/10.1021/ol501459e | *Org. Lett.* 2014, 16, 3524−3527

Scheme 3. A Proposed Mechanism



could be stabilized by a carbonyl oxygen of the Boc protecting group. Subsequent insertion into the second terminal alkyne followed by reductive elimination then gives the enyne **3**.

In conclusion, in the effort described above we have developed a novel microwave-assisted tandem Heck−Sonogashira reaction of 6-*N*,*N*-di-Boc-amino-5-iodo-2-methylpyrimidin-4-ol that forms functionalized enyne (−C═C−C≡C−) substituted pyrimidines. The products of this process undergo ready cyclization to generate novel substituted pyrido[2,3-*d*]pyrimidines in good to excellent yields. Notably, the enyne forming and cyclization sequence is applicable to the synthesis of a variety of novel highly functionalized fused pyridines. Further studies are underway to show that this chemistry is applicable to the preparation of heterocycle libraries for high throughput screening efforts.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for all new compounds and crystal structure data for **3af** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support of this research provided by the National Natural Science Foundation of China (81225022) and SA-SIBS Scholarship Program is gratefully acknowledged.

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