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PII: S0040-4039(15)00741-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.04.094
Reference: TETL 46234

To appear in: *Tetrahedron Letters*

Received Date: 17 March 2015
Revised Date: 19 April 2015
Accepted Date: 22 April 2015

Please cite this article as: Bellina, F., Lessi, M., Marianetti, G., Panattoni, A., Highly regioselective C-5 Alkynylation of Imidazoles by One-pot Sequential Bromination and Sonogashira Cross Coupling, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.04.094

Graphical Abstract

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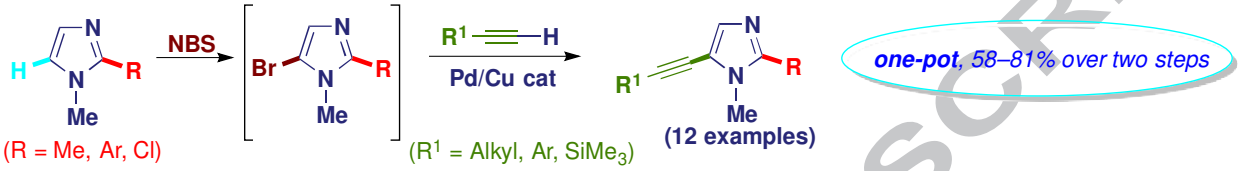

Tetrahedron Letters
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Highly regioselective C-5 Alkynylation of Imidazoles by One-pot Sequential Bromination and Sonogashira Cross Coupling

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Imidazoles
Sonogashira reaction
Regioselectivity
Aromatic Bromination
Alkynylation

ABSTRACT

A variety of 2-substituted 5-alkynyl-1*H*-imidazoles was easily prepared by a one-pot sequential procedure involving a highly regioselective electrophilic C-5 bromination of 1,2-dimethyl-1*H*-imidazole, 2-chloro-1-methyl-1*H*-imidazole, and 2-aryl-1-methyl-1*H*-imidazoles, followed by an efficient palladium/copper co-catalyzed Sonogashira-type alkynylation.

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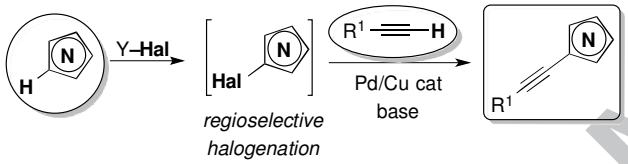
1. Introduction

Alkynyl-substituted azoles represent important structural cores of several biologically active molecules[1] and organic functional materials.[2] The most classical method for the preparation of heteroarylalkynes relies on the Sonogashira-Hagihara coupling, in which heteroaryl halides (generally iodides or the less reactive bromides) and terminal alkynes are reacted under a combined palladium-copper co-catalysis.[3,4] More recently, direct alkynylation procedures, that substantially invert the synthetic disconnection employing heteroarenes and alkynyl halides as coupling partners have been proposed as a viable alternative to classical Sonogashira coupling.[5] However, these protocols suffer from limited scopes due to the fact that not all the CH bonds are reactive, and directing groups are sometimes required to prevent regioselectivity issues. These approaches may be both described as CH-CX bond coupling, but from an atom-economy viewpoint it would be better to employ unfunctionalized coupling partners coupling two CH bonds. Several recent examples of this last procedure involving alkynes and azoles have been published, but unfortunately both their scope and regioselectivity are limited.[6]

Recently, during our studies on the direct functionalization of azoles,[7] we became interested in the regioselective preparation of alkynyl-substituted azoles as scaffolds for new synthetic dyes,[2b,8] and we argued that a CH-CH coupling could be achieved by a combination of a regioselective electrophilic halogenation with a classical Sonogashira coupling (Scheme 1).



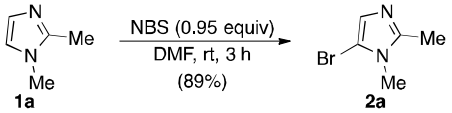
Scheme 1. One-pot sequential halogenation-alkynylation of azoles

In this communication we report the application of this synthetic approach to the regioselective efficient synthesis of 2-substituted 5-alkynylimidazoles through an unprecedented one-pot electrophilic bromination of 2-substituted imidazoles followed by a palladium and copper co-catalyzed alkynylation reaction.[9] This procedure allowed a highly regioselective Csp-Csp2 coupling involving unactivated coupling partners.

2. Results

2.1. Optimization of the bromination step

In principle, we devoted our efforts to re-examination of the electrophilic bromination of imidazoles, since we needed a highly regioselective and efficient procedure that could be compatible with Pd/Cu-catalyzed alkynylation, and no efficient synthetic method was known. All the reported procedures for the electrophilic bromination of imidazoles show in fact that clear monobromination of imidazoles is rarely achieved, and mixtures of brominated and/or polybrominated isomers are often obtained.[10] Our preliminary screening on suitable reaction conditions for subsequent Sonogashira coupling proved that any attempt to selectively brominate at *N*-1 or *C*-2 unsubstituted imidazoles led to complex mixtures of brominated imidazoles (Table S1, Supporting Information). However, to our delight we found that treating 1,2-dimethyl-1*H*-imidazole (**1a**) with 0.95 equiv of NBS in DMF at room temperature for 3 h led to the regioselective formation of 5-bromo-1-methyl-1*H*-imidazole (**2a**) in 89% isolated yield (Scheme 2).

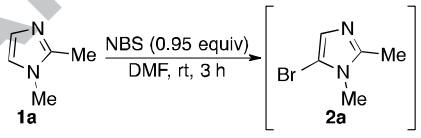


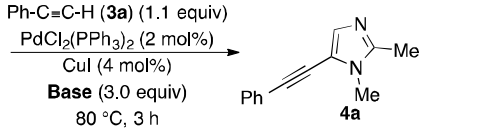
Scheme 2. Regioselective C-5 bromination of 1,2-dimethyl-1*H*-imidazole (**1a**)

We also found that a base such as potassium carbonate, previously employed mainly to remove residual HBr from NBS,[11] was not required when freshly recrystallized NBS was used.

2.2. One-pot sequential C-5-bromination and Sonogashira coupling

Once optimal conditions for the regioselective C-5 bromination were found, efforts were then devoted to verify the possibility of pairing the halogenation with a Sonogashira alkynylation to obtain directly 5-alkynylimidazoles from the parent azole derivative. At first, we tried the same reaction conditions previously employed by us for the alkynylation of electron-poor bromoarenes.[2b] Hence, to 5-bromoimidazole **2a** in DMF, resulting from the bromination of **1a** with 0.95 equiv NBS as previously described, 1.1 equiv of phenylacetylene (**3a**), 2 mol% $PdCl_2(PPh_3)_2$, 4 mol% CuI, and 3 equiv of Et_3N were sequentially added. The reaction temperature was then raised to 80 °C, and after 3 h the required 5-alkynylimidazole **4a** was isolated in a satisfactory 58% yield (Scheme 3).



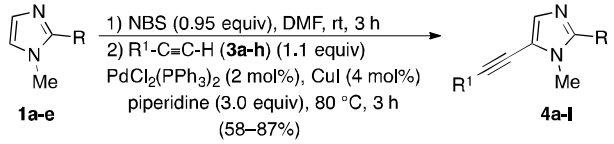


Base	Isolated Yield (%)
Et_3N	58
Piperidine	71

Scheme 3. One-pot bromination-alkynylation of imidazole **1a**

With the aim of further improving this preliminary result, we set up a quick screening of the base, and we found that the use of piperidine instead of Et_3N raised the yield of **4a** up to 71% (Scheme 3). In contrast, the use of other bases commonly employed in Sonogashira alkynylations, such as DBU, *n*-$BuNH_2$, or *i*$PrEt_2N$, gave unsatisfactory results.

The good results obtained in the preparation of **4a** from **1** and **3a** prompted us to extend this efficient procedure to the selective preparation of a variety of 2-substituted 5-alkynylimidazoles starting from the corresponding 2-substituted azoles and alkynes (Scheme 4).



Scheme 4. One-pot bromination-alkynylation of imidazoles **1a-e** with alkynes **3a-h**

From the data reported in Table 1, it emerged that aromatic and aliphatic alkynes are able to react with 5-bromo-1,2-dimethyl-*1H*-imidazole (**2a**) formed in situ, allowing the isolation of the corresponding 5-alkynyl substituted derivatives in good to satisfactory yields (entries 1–8, Table 1). In details, phenylacetylene (**3a**) gave the desired product **4a** in 71% isolated yield (Scheme 3 and entry 1, Table 1).

Table 1. Synthesis of 2-substituted 5-alkynylimidazoles **4a-l** via one-pot sequential bromination-Sonogashira coupling involving 2-substituted imidazoles **1a-e** and alkynes **3a-h**.

Entry[a]	Imidazole		Alkyne		Product	
	1	R	**3**	R^1	**4**	Isolated yield(%)
1	**1a**	Me	**3a**	C_6H_5	**4a**	71
2	**1a**	Me	**3b**	4-$MeOC_6H_4$	**4b**	81
3	**1a**	Me	**3c**	4-$F_3CC_6H_4$	**4c**	68
4	**1a**	Me	**3d**	*n*-C_4H_9	**4d**	58
5	**1a**	Me	**3e**	*n*-$C_{10}H_{21}$	**4e**	63
6	**1a**	Me	**3f**	2-cyclohexen-1-yl	**4f**	77
7	**1a**	Me	**3g**	4-hydroxybut-1-yl	**4g**	66
8[b]	**1a**	Me	**3h**	Me_3Si	**4h**	63
9	**1b**	4-MeC_6H_4	**3a**	C_6H_5	**4i**	58
10	**1c**	4-$MeOC_6H_4$	**3a**	C_6H_5	**4j**	87
11[c]	**1d**	4-$EtOOCC_6H_4$	**3a**	C_6H_5	**4k**	74
12	**1e**	Cl	**3a**	C_6H_5	**4l**	68

(a) Unless otherwise stated, the reactions were performed using 1 mmol of **1** in 5 mL of DMF; the bromination step was carried out with 0.95 equiv of NBS for 3 h at room temperature, and the alkynylation step for 3 h at 80 °C using 1.1 equiv of **3**, 2 mol% $PdCl_2(PPh_3)_2$, 4 mol% CuI, and 3.0 equiv of piperidine. (b) The alkynylation step was performed at 50 °C. (c) This reaction required 24 h to go to completion.

The 5-bromo intermediate **2a** underwent the alkynylation step in good yield when either electron-donating or electron-withdrawing groups were present on the ethynylarenes. As a matter of fact **4b**, derived from the reaction of **2a** with ethynylanisole (**3b**), was isolated in 81% yield (entry 2, Table 1), while the electron-poor alkyne **3c** provided the alkynylated compound **4c** in 68% isolated yield (entry 3, Table 1). Typical aliphatic alkynes such as 1-hexyne (**3d**) and 1-dodecyne (**3e**) were also efficiently coupled, and gave the respective 5-alkynyl-1,2-dimethyl-1*H*-imidazoles **4d** and **4e** in 58% and 63% isolated yields, respectively (entries 4 and 5, Table 1). The reaction worked well also when a typical conjugated enyne, **3f**, was employed: the required coupling product **4f** was recovered in 77% yield (entry 6, Table 1). Free hydroxyl groups are also well tolerated, as demonstrated by the reaction involving 5-hexyn-1-ol (**3g**), which gave the required substituted imidazole **4g** in a satisfactory 66% isolated yield (entry 7, Table 1). On the contrary, when trimethylsilylacetylene (**3h**) was employed as the alkyne the reaction was not so efficient due to an extensive desilylation, which led to a complex reaction mixture. Fortunately, lowering the reaction temperature to 50°C reduced the desilylation and allowed us to recover the desired product **4h** in a 63% isolated yield (entry 8, Table 1). An attempt to perform the one-pot bromination/alkynylation reaction employing ethyl propiolate as the alkyne was also made, but only the nucleophilic addition of piperidine on the unsaturated ester occurred.

In order to further expand the scope of this method, some typical 2-aryl substituted imidazoles were submitted to the optimized one-pot bromination-alkynylation sequence, as summarized in Table 1. Similarly to what observed for 1,2-dimethylimidazole, 2-arylimidazoles **1b–d** were easily brominated at their *C*-5 position. Electron-donating or electron withdrawing groups did not significantly affect the rate and selectivity of this step, as they did not influence the chemical yield of the entire synthetic sequence (entries 9-11, Table 1). However, the electronic nature of the C-2 aromatic substituent influenced the rate of the second step and, in particular, it was observed that electron-poor groups strongly slowed down the reaction. In fact **1d**, after conversion into the corresponding 5-bromoderivative **2d**, required 24 h at 80 °C to furnish the 5-alkynyl substituted derivative **4k** (entry 11, Table 1), while the same reaction involving **1b** and **1c**, bearing at their C-2 electron-donor groups, required only 3 h at the same temperature (entries 9 and 10, Table 1).

As stated before, it is not possible to perform a clean C-5 bromination on the imidazole ring when C-2 position is free. Hence, we thought it appropriate to try our method on some imidazoles protected at C-2 with groups that could be easily removed after the C-5 bromination-alkynylation synthetic sequence. Firstly, we employed 2-chloro-5-methyl-1*H*-imidazole (**1e**) as precursor, whose chlorine atom may be removed by direct reduction,[12] or by metallation and subsequent hydrolysis.[13] As we hoped for, the alkynylation of the intermediate 5-bromo-2-chloro-1-methyl-1*H*-imidazole obtained by bromination of **1e** provided the desired 5-alkynylated compound **4l** in 68% yield over two steps (entry 12, Table 1). The chlorine atom on the C-2 position did not affect the rate of the halogenation step, which provided the C-5 brominated intermediate as the only reaction product in 3 h. The alkynylation step also was not affected by the

presence of the chlorine atom, and the reaction proceeded selectively at the C-Br bond.

Unfortunately, the possibility of employing an ester group or a trialkylsilyl group to protect C-2 revealed to be impracticable. In fact, when ethyl 1-methyl-1*H*-imidazole-2-carboxylate (**1f**) or 2-(*tert*-butyldimethylsilyl)-1-methyl-1*H*-imidazole (**1g**) were used, the halogenation step provided an almost equimolar mixture of two mono-brominated products (4- and 5-bromo derivatives). Moreover, during the attempted alkynylation step partial decarboxylation or desilylation occurred.

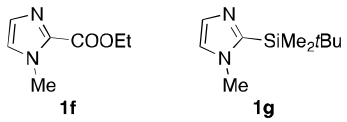


Figure 1. Chemical structure of imidazoles **1f** and **1g**

3. Conclusions

In summary, an effective one-pot strategy for the direct alkynylation of imidazoles with alkynes has been developed. Through a careful choice of the reaction conditions, we were able to obtain the regioselective C-5 monobromination of 2-substituted imidazoles, including 2-chloroimidazole, and to successfully pair this reaction with an effective Sonogashira coupling with functionalized alkynes, allowing us to obtain several 2-substituted 5-alkynylimidazoles in high yields. In the next future, we are planning to apply this unprecedented one-pot procedure to the synthesis of new classes of imidazole-based organic dyes.

Acknowledgments

This study was supported by the Università di Pisa under PRA 2015 (project no. 2015_0038) and by MIUR-FIRB (RBFR122HFZ).

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Supplementary Material

Experimental procedures and characterization for compounds **1b–g**, **2a**, **4a–l**, and preliminary screening of bromination with NBS of 1,2-methyl-1*H*-imidazole (**1a**) may be found, in the online version, at http://dx.doi.org/10.1016/tetlet00000000