A Simple and Efficient Copper-Catalyzed Synthesis of *N*-Alkynylimidazoles

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Abstract: A simple and efficient method for the synthesis of *N*-alkynylheteroarenes from 1,1-dibromo-1-alkenes was developed via a copper-catalyzed cross-coupling reaction. Generally superior yields and functional-group tolerance were obtained with TMEDA as ligand using imidazole and benzimidazole substrates in dioxane.

Key words: *N*-alkynylimidazoles, 1,1-dibromo-1-alkenes, copper, cross-coupling reaction, alkynylation

Metal-catalyzed cross-coupling reactions are among the most powerful methods available for the formation of carbon–carbon and carbon–heteroatom bonds.[1,2] On the other hand, *gem*-dibromoolefins serve as important synthetic intermediates in a variety of transformations,[2] the most famous one probably being the Corey–Fuchs alkyne synthesis.[3] More recently, their reactivity in transition-metal-mediated reactions was investigated, 1,1-dibromo-1-alkenes have been shown to be especially useful substrates for palladium and copper catalysis since they participate in a number of coupling reactions, and these procedures have been used for the formation of a number of compounds.[4]

N-Alkynylheteroarenes are an interesting variation on ynamines and share with ynamides the increased stability engendered by delocalization of the lone pair of electrons on the nitrogen atom,[5] which are functional groups that possess significant potential in organic chemistry for the formation of carbon–carbon bonds yet underutilized intermediates in organic synthesis[6] and medicinal chemistry.[7] The underlying reason is the dearth of mild and general preparative methods of their formation. Current preparative methods for the synthesis of *N*-alkynylheteroarenes include elimination from haloenamines[8] or enol triflates,[9] isomerization of propargyl groups,[10] and coupling with alkynyl iodonium salts.[11] More recently, a modern variant for the synthesis of *N*-alkynylheteroarenes has been developed, which is based upon transition-metal-mediated coupling of N-heterocycles with bromoalkynes using conventional heating protocols or microwave-assisted ones.[12] However, all these methods suffer from either limited substrate scope or formation of direct nucleophilic addition side products.[12b,c] Therefore, the development of a general and efficient method for the preparation of *N*-alkynylheteroarenes is still highly desirable. Drawing from recent experiences in the field of copper-catalyzed cross-coupling reactions,[1] and initially inspired by the work of Evano's group in the copper-catalyzed N-alkynylation[1d] of amides, we thought that an attractive alternative for the preparation of *N*-alkynylheteroarenes could be performed using catalytic amounts of copper(I) salts from readily available 1,1-dibromo-1-alkyenes and their further reaction with the appropriate N-containing heterocycles. Herein, we report a simple and facile method for the synthesis of *N*-alkynylheteroarenes incorporating the imidazole and benzimidazole heterocyclic cores.

Initially, imidazole (**1a**) and (2,2-dibromovinyl)benzene (**2a**) were selected as the model substrates in search of a better protocol. Under the reported conditions,[1d] the reaction of imidazole (**1a**) with (2,2-dibromovinyl)benzene (**2a**) and CuI in dioxane gave 1-(phenylethynyl)-1*H*-imidazole **3a**[13] in 41% yield (Table 1, entry 1); performing the same reaction at 80 °C provided a 66% yield of the desired product, together with a small amount of homocoupling product **4** (Table 1, entry 2). To our delight, with TMEDA as ligand instead of DMEDA, amination product **3a** was isolated in 82% yield, and none of the undesired byproducts was observed (Table 1, entry 3); however, a further increase in the reaction temperature from 80 °C to reflux is detrimental. Under reflux conditions, fast disappearance of the (2,2-dibromovinyl)benzene is accompanied by the formation of the homocoupling product (Table 1, entry 4,). After screening the amounts of base and CuI, it was observed that four equivalents of base and 0.05 equivalents of CuI are the best (Table 1, compare entries 5 and 6); other solvents and bases such as DMF or K_3PO_4 led to a low yield (Table 1, entries 7–9). CuI exhibited superior catalytical efficiency over all other examined Cu catalysts (Table 1, entries 10 and 11). Thus, the abovementioned reactions with CuI and TMEDA provided to be the best for the alkynylation of imidazoles to furnish the desired *N*-alkynylimidazoles with little or no formation of the homocoupled bisalkyne byproducts.

The scope of the copper-catalyzed alkynylation was examined by reacting **1a** with a variety of 1,1-dibromo-1-alkenes. As shown in Table 2, under the optimized conditions (5 mol% of CuI, 10 mol% *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) the alkynylation of imidazole **1a** with **2** appeared to be quite general with respect to the substituents. Thus, 1,1-dibromoalkenes bearing electron-donating and electron-withdrawing groups were smoothly aminated to give *N*-alkynylimidazoles **3a**–**g** in moderate to good yields. Electron-deficient substrates gave better yields. Aromatic halides are tolerated, and no amination was observed, so that this offers additional opportunity for fur-

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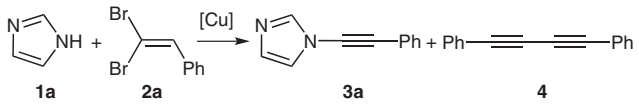
Table 1 Optimization of the Copper-Catalyzed *N*-Alkynylation of Imidazole with (2,2-Dibromovinyl)benzene[a]



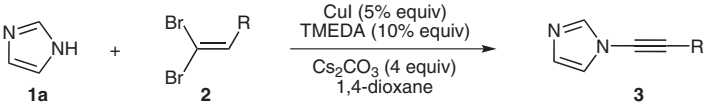
1a **2a** **3a** **4**

Entry	Catalyst (mol%)	Ligand[b]	Base (equiv)	Solvent	Temp (°C)	Yield of **3a** (%)[c]	Yield of **4** (%)[c]
1	CuI (5)	DMEDA	Cs_2CO_3 (4)	dioxane	60	41	0
2	CuI (5)	DMEDA	Cs_2CO_3 (4)	dioxane	80	66	3
3	CuI (5)	TMEDA	Cs_2CO_3 (4)	dioxane	80	82	0
4	CuI (5)	TMEDA	Cs_2CO_3 (4)	dioxane	102 (reflux)	67	14
5	CuI (10)	TMEDA	Cs_2CO_3 (4)	dioxane	80	77	2
6[d]	CuI (5)	TMEDA	Cs_2CO_3 (2)	dioxane	80	29	3
7	CuI (5)	TMEDA	Cs_2CO_3 (4)	DMF	80	50	12
8	CuI (5)	TMEDA	Cs_2CO_3 (4)	toluene	80	27	0
9	CuI (5)	TMEDA	K_3PO_4 (4)	dioxane	80	73	4
10	CuO (5)	TMEDA	Cs_2CO_3 (4)	dioxane	80	trace	9
11	CuCl (5)	TMEDA	Cs_2CO_3 (4)	dioxane	80	19	23

[a] Reactions were carried out using imidazole (1 mmol), (2,2-dibromovinyl)benzene (1.5 mmol), and ligand (0.1 mmol) in solvent (2 mL) for 24 h under N_2.
[b] TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DMEDA = *N*,*N*′-dimethylethanediamine.
[c] Yields of isolated products after chromatographic purification.
[d] Reaction run at 80 °C for 48 h.

ther functionalization. It is worth noting that the olefins bearing heteroaryl groups can also be smoothly transformed to the desired products in good yields (Table 2, entries 8 and 9). In contrast to the aromatic alkenes, the coupling reaction of linear aliphatic olefins provided the corresponding *N*-alkynylimidazoles as well but need a longer reaction time (Table 2, entry 10). We found, however, that vinyl 1,1-dibromoalkenes such as 1,1-dibromo-4-methylpenta-1,3-diene, which are definitely not the best reaction partners in copper-catalyzed cross-coupling reactions, were not suitable substrates (Table 2, entry 11).

Table 2 Copper-Catalyzed Alkynylation of Imidazole with 1,1-Dibromo-1-alkenes[a]



1a **2** **3**

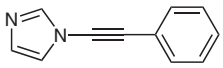
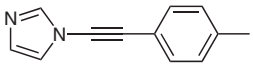
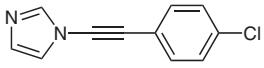
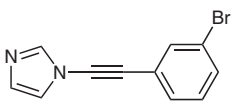
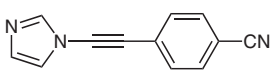
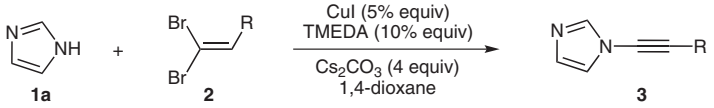
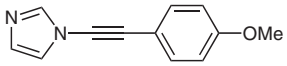
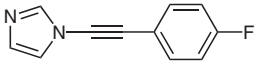
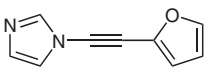
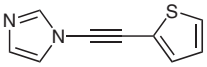
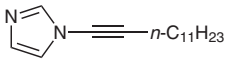
Entry	R	Product	Yield (%)[b]
1	Ph **2a**		**3a** 82
2	4-MeC_6H_4 **2b**		**3b** 78
3	4-ClC_6H_4 **2c**		**3c** 80
4	3-BrC_6H_4 **2d**		**3d** 76
5	4-NCC_6H_4 **2e**		**3e** 81

Table 2 Copper-Catalyzed Alkynylation of Imidazole with 1,1-Dibromo-1-alkenes[a] (continued)



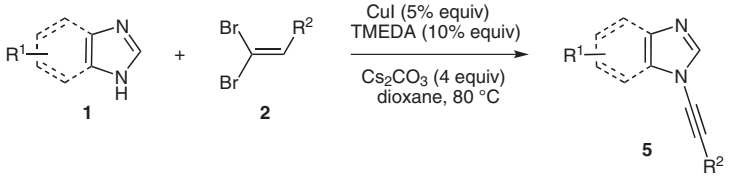
1a + **2** → **3**

Entry	R	Product	Yield (%)[b]
6	4-$OMeC_6H_4$ **2f**		**3f** 65
7	4-FC_6H_4 **2g**		**3g** 84
8[c]	2-furyl **2i**		**3h** 79
9	2-thienyl **2j**		**3i** 83
10[d]	*n*-$C_{11}H_{23}$ **2k**		**3j** 45
11[d]	 **2l**		n.r.[e]

[a] Conditions: **1a** (1.0 mmol) and **2** (1.5 mmol) at 80 °C for 24 h, under N_2.
[b] Yields of isolated products after chromatographic purification.
[c] Reaction run at 60 °C.
[d] Reaction run at 80 °C for 48 h.
[e] No reaction.

The coupling of imidazoles bearing different substituents with various 1,1-dibromo-1-alkenes **2** was investigated next under the optimized reaction conditions (Table 3). In general, the substituted imidazoles could be successfully used in this copper-mediated cross-coupling reaction to give the desired products in moderate to good yields. For example, when 2-methylimidazole was used, good yields of the *N*-alkynylheteroarenes derived from the coupling of the 1,1-dibromoalkenes **2a**,**b**,**d** were observed (Table 3, entries 6–8). The reaction was, however, found to be rather general and allowed for the synthesis of a wide range of *N*-alkynylimidazoles possessing ethyl, propyl, isopropyl, and benzo[*d*] substituting groups. In the case of 4-methylimidazole (Table 3, entry 20), coupling with **2a** gave a 7:1 mixture of regioisomeric *N*-alkynylimidazoles **5ta** and **5tb**. The regiochemistry of the major isomer **5ta** was established as 1,4 by NMR spectroscopy.

Table 3 Copper-Catalyzed Alkynylation of Imidazole and Benzimidazole with 1,1-Dibromo-1-alkenes[a]



1 + **2** → **5**

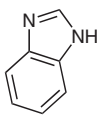
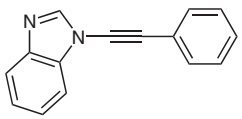
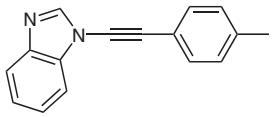
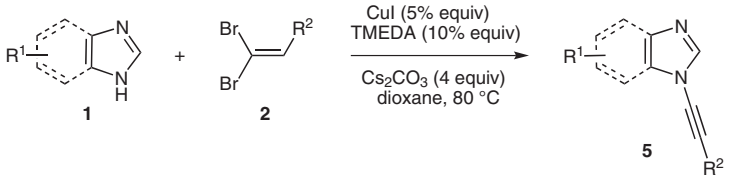
Entry	**1**	R^2	Product	Yield (%)[b]
1	 **1b**	Ph **2a**		**5a** 79
2	**1b**	4-MeC_6H_4 **2b**		**5b** 70

Table 3 Copper-Catalyzed Alkynylation of Imidazole and Benzimidazole with 1,1-Dibromo-1-alkenes[a] (continued)



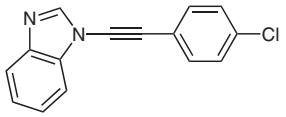
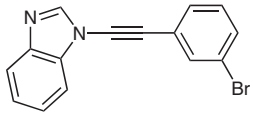
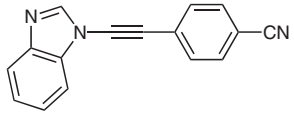
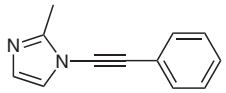
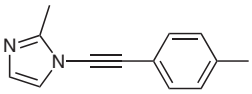
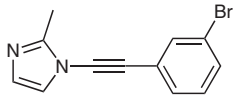
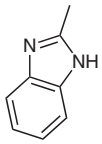
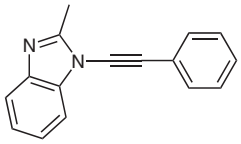
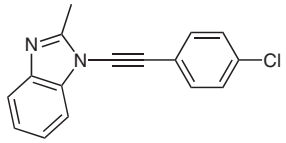
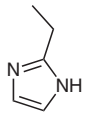
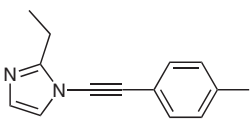
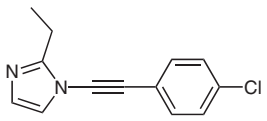
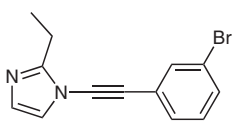
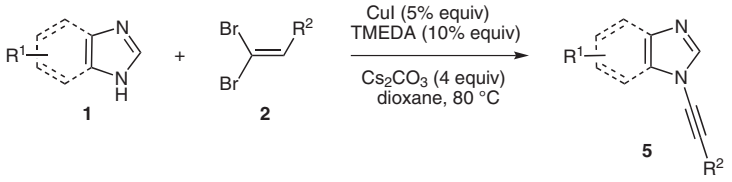
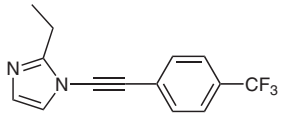
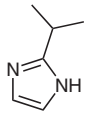
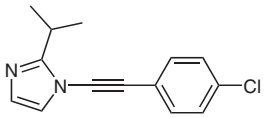
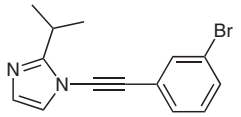
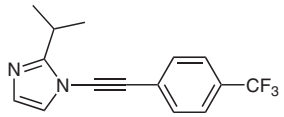
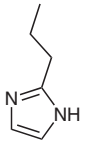
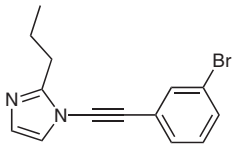
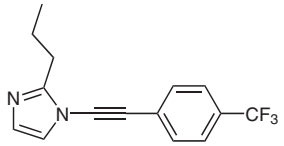
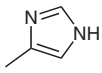
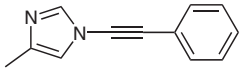
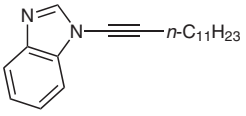
Entry	1	R^2	Product	Yield (%)[b]
3	**1b**	4-ClC_6H_4 **2c**		**5c** 81
4	**1b**	3-BrC_6H_4 **2d**		**5d** 72
5	**1b**	4-NCC_6H_4 **2e**		**5e** 82
6	 **1c**	Ph **2a**		**5f** 67
7	**1c**	4-MeC_6H_4 **2b**		**5g** 66
8	**1c**	3-BrC_6H_4 **2d**		**5h** 71
9	 **1d**	Ph **2a**		**5i** 68
10	**1d**	4-ClC_6H_4 **2c**		**5j** 80
11	 **1e**	4-MeC_6H_4 **2b**		**5k** 76
12	**1e**	4-ClC_6H_4 **2c**		**5l** 70
13	**1e**	3-BrC_6H_4 **2d**		**5m** 81

Table 3 Copper-Catalyzed Alkynylation of Imidazole and Benzimidazole with 1,1-Dibromo-1-alkenes[a] (continued)



Entry	1	R^2	Product	Yield (%)[b]
14	**1e**	4-$F_3CC_6H_4$ **2h**		**5n** 69
15	 **1f**	4-ClC_6H_4 **2c**		**5o** 55
16	**1f**	3-BrC_6H_4 **2d**		**5p** 78
17	**1f**	4-$F_3CC_6H_4$ **2h**		**5q** 60
18	 **1g**	3-BrC_6H_4 **2d**		**5r** 77
19	**1g**	4-$F_3CC_6H_4$ **2h**		**5s** 58
20	 **1h**	Ph **2a**		**5t** 71[c] (**5ta**/**5tb** = 7:1)[d]
21[e]	**1b**	*n*-$C_{11}H_{23}$ **2k**		**5u** 39

[a] Conditions: **1** (1.0 mmol) and **2** (1.5 mmol) at 80 °C for 24 h, under N_2.
[b] Yields of isolated products after chromatographic purification.
[c] GC yield.
[d] The ratio of the isomeric products was determined by GC.
[e] Reaction run at 80 °C for 48 h.

In summary, a copper-mediated synthesis of *N*-alkynylimidazoles has been described. This reaction has been shown to be general and provides a straightforward entry to *N*-alkynylheteroarenes from readily available 1,1-dibromo-1-alkenes. Further studies in this area are being conducted in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **Typical Procedure for the Synthesis of *N*-Alkynylimidazole**

A vessel with a magnetic stir bar was charged with imidazole (**1a**, 68 mg, 1 mmol), CuI (10 mg, 0.05 mmol), Cs_2CO_3 (1.3 g, 4 mmol), and TMEDA (12 mg, 0.1 mmol) under a nitrogen atmosphere. The reaction vessel was evacuated and backfilled with nitrogen three times. In a separate flask, a solution of dry dioxane (2 mL) containing the (2,2-dibromovinyl)benzene (**2a**, 1.5 mmol) was evacuated and back-filled with nitrogen gas three times. The dioxane solution was then added to the reaction flask with a syringe, and the reaction mixture was heated to 80 °C for 24 h. The reaction mixture was cooled to r.t., quenched with a sat. NH_4Cl solution (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over anhyd Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography with EtOAc and PE (1:4) as eluent to afford the 1-(phenylethynyl)-1*H*-imidazole (**3a**) as a yellow oil; yield 82%. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (s, 1 H), 7.61–7.45 (m, 2 H), 7.42–7.32 (m, 3 H), 7.20 (d, *J* = 1.1 Hz, 1 H), 7.09 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.2, 131.9, 129.4, 129.2, 128.7, 121.9, 78.2, 70.6. ESI-MS: *m/z* = 169.1 $[M + H]^+$.

