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Coupling Reactions of Bromoalkynes with Imidazoles Mediated by Copper Salts: Synthesis of Novel *N*-Alkynylimidazoles

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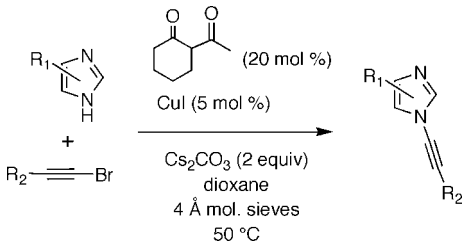

A cross-coupling reaction of imidazoles with bromoalkynes in the presence of a catalytic amount of CuI is reported. This protocol allows an access to novel *N*-(1-alkynyl)imidazoles in moderate to good yields.

N-Alkynylheteroarenes are an interesting variation on ynamines and share with ynamides the increased stability engendered by delocalization of the nitrogen lone pair.[1] Despite a few reports of interesting biological[2] and photoconductive[3] properties, this entire class of molecules remains largely unexplored. This may be explained by the lack of a general and mild synthetic route to these compounds. Current methods involving elimination from haloenamines[4] or enol triflates,[5] isomerization of propargyl groups,[6] or coupling with alkynyl iodonium salts[7] all suffer limitations in scope.

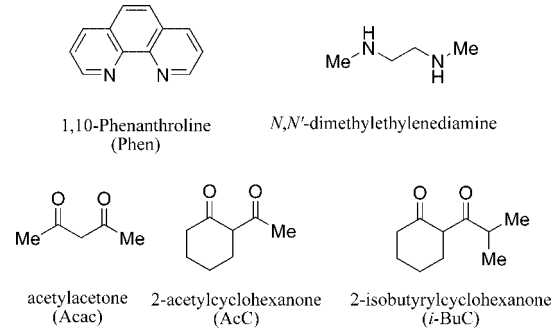

FIGURE 1. Ligands used in this work.

One class of *N*-alkynylheteroarenes that has received recent attention are the 1,2-dialkynylimidazoles, which have been studied as aza analogues of diradical-generating enediynes.[8] Unfortunately, the synthesis of such *N*-alkynylimidazole moieties via alkynyliodonium salt chemistry gives poor yields and presents a limited scope.[8] Recent advances in copper-catalyzed amination of aryl halides, including *N*-arylations of imidazole[9] and diverse *N*-alkynylation reactions of sulfonamides,[10–13] amides,[11,13] ureas,[11–13] indoles,[11–13] or carbamates[11–13] mediated by copper complexes inspired the work described here, which has led to the first copper-catalyzed alkynylation of imidazoles by alkynyl halides.

Initial attempts to couple imidazole with bromophenylacetylene employed conditions similar to Hsung's protocol[11] for *N*-alkynylations of amides using 1,10-phenanthroline (Figure 1) as ligand and $CuSO_4 \cdot 5H_2O$ as copper source, and Sato's protocol[10,14] for *N*-alkynylation of sulfonamides using *N*,*N*′-dimethylethylenediamine (Figure 1) as ligand and CuI as copper source yielded only traces of the expected *N*-alkynylimidazole. In contrast, by using 2-acetylcyclohexanone (AcC, Figure 1)

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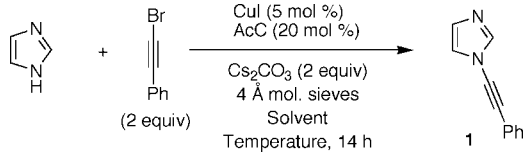
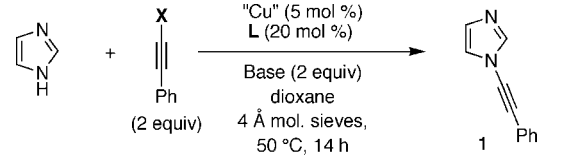
TABLE 1. Solvent and Temperature Effects on the Imidazole Alkynylation Reaction[a]



entry	solvent	T (°C)	yield[b] (%)
1	DMF	rt[c]	26
2	DMF	50	40
3	toluene	rt[c]	0
4	toluene	50	39
5	toluene	110 (reflux)	12
6	THF	rt[c]	23
7	THF	50	43
8	DME	rt[c]	18
9	DME	50	39
10	DMSO	rt[c]	41
11	DMSO	50	36
12	dioxane	rt[c]	8
13	dioxane	50	52
14	dioxane	101 (reflux)	49

[a] Reactions carried out on 1 mmole scale in 2 mL of solvent under argon. [b] Isolated yield after column chromatography. [c] Room temperature, approximately 20 °C.

TABLE 2. Condition Optimization of the Imidazole Alkynylation Reaction[a]



entry	X	base	ligand (L)[b]	"Cu"	yield[c] (%)
1	Br	Cs_2CO_3	AcC	CuI	52
2	I[16]	Cs_2CO_3	AcC	CuI	2
3	Cl[17]	Cs_2CO_3	AcC	CuI	15
4	Br	K_3PO_4	AcC	CuI	6
5	Br	K_2CO_3	AcC	CuI	1
6	Br	*t*-BuOK	AcC	CuI	30
7	Br	LHMDS	AcC	CuI	9
8	Br	Cs_2CO_3	None	CuI	10
9	Br	Cs_2CO_3	*i*-BuC	CuI	26
10	Br	Cs_2CO_3	acac	CuI	2
11	Br	Cs_2CO_3	Phen	CuI	7
12	Br	Cs_2CO_3	AcC	CuCl	57
13	Br	Cs_2CO_3	AcC	CuCN	44
14	Br	Cs_2CO_3	AcC	$CuSO_4$	39

[a] Reactions carried out on 1 mmole scale in 2 mL of solvent under argon. [b] See Figure 1 for the structures of the ligands. [c] Yields of isolated products after chromatographic purification.

as ligand and CuI as the copper source[15] in DMF at room temperature, the *N*-alkynylimidazole was formed in moderate yield. A screen of various solvent and temperature conditions (Table 1) demonstrates that with the exception of toluene, all of the solvents examined provided at least low yields of the *N*-alkynylimidazole at room temperature. With the exception of reactions run in DMSO, an increase in reaction temperature from room temperature to 50 °C leads to an increase in yield; however, for toluene and dioxane, a further increase in temperature to reflux is detrimental. Under reflux conditions, as in DMSO at 50 °C, fast disappearance of the bromoalkyne is accompanied by the formation of the homocoupling product. Thus, dioxane appears to be the optimal solvent for this transformation, and DMSO is a possible alternative at room temperature.

After optimizing the solvent, a second set of reactions were carried out to ascertain the effects of different bases, copper sources, ligands, and haloalkyne partners (Table 2). On the basis of the reaction with three different halo(phenyl)acetylenes, only bromoacetylenes undergo coupling in good yield (entry 1−3). Cesium carbonate appears to be the base of choice for this coupling reaction. Here, this system presents a different reactivity than the alkynylation reactions developed by Hsung[11] or Sato[10] where K_3PO_4 and K_2CO_3 are, in both cases, bases of choice for the transformation.[16] These results are not consistent with a problem of base strength but can be explained by superior solubility of Cs_2CO_3 in dioxane at 50 °C.

Without added ligand, the reaction proceeds, but only in 10% yield (Table 2, entry 8). We surmise that imidazole itself can serve as ligand, similar to what is observed in copper-mediated arylation reactions.[17] However, without any copper catalyst present, no reaction is observed (in DMF). Replacing the 2-acetylcyclohexanone ligand by acetylacetate (acac) or 2-isobutyrylcyclohexanone (*i*-BuC) leads to a decrease in yield, in contrast to the case for the copper-mediated aryl amination reported by Buchwald,[15] in which *i*-BuC is the superior ligand. Additionally, 1,10-phenanthroline (Phen, entry 11), though suitable for numerous alkynylation reactions and imidazole arylations, is ineffective under our reaction conditions. The coupling shows little influence on the source of copper; either copper(I) or copper(II) species can be used.

A variety of imidazole and bromoacetylene coupling partners were examined. In order to avoid problems with less reactive reagent pairs, the consumption of bromoalkyne by TLC was monitored after the reaction mixtures were stirred for 14 h at 50 °C, and if necessary, the mixtures were then heated under reflux for 4 h. The coupling reactions of unsubstituted imidazole and benzimidazole were successfully achieved in good to moderate yield with aryl, alkyl, and silylated bromoalkynes (Table 3, entries 1−3, 6−8). In the case of the *tert*-butyldimethylsilyl-protected bromopropargyl alcohol (entry 4), the low yield of *N*-alkynylimidazole could be explained by the formation of a side product, the bromoalkene **16** (Figure 2) in 20% yield.[18] This direct nucleophilic addition of the imidazole anion to the bromoalkyne is not observed for the more hindered, dimethyl-substituted propargylic alcohol coupling partner (entry 5).

In the case of 4-phenylimidazole, coupling with bromophenylacetylene affords a 9:1 mixture of regioisomeric *N*-alkynylimidazoles **9a**,**b**. The regiochemistry of the major isomer **9a** was established as 1,4 by conversion to the haloalkene **17** (Figure 2), the structure of which was established by ^{1}H NOE analysis (Supporting Information). In the case of other bromoacetylenes (Table 3, entries 10 and 11), the regioselectivity is excellent and only the 1,4-regioisomers were observed. This

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(16) We noticed that during the solvent screening (Table 1) the reactions with K_3PO_4 or Cs_2CO_3 afforded the product with the same yield at room temperature in DMF (26% in both cases) and that these reactions were not very sensitive to the equivalents of base added; see the Supporting Information.

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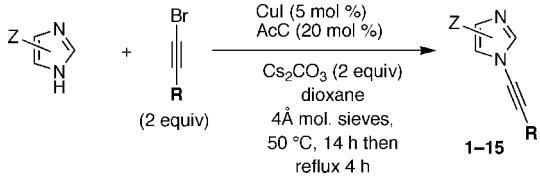
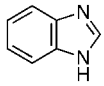
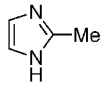
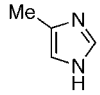
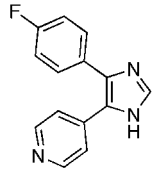
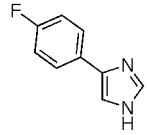
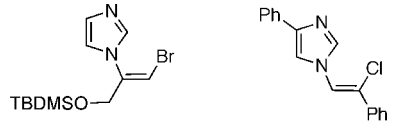
(18) The alkene stereochemistry of **15** was elucidated by ^{1}H nuclear Overhauser enhancement experiments (see the Supporting Information).

TABLE 3. Preparation of *N*-Alkynylimidazoles 1−15[a]



entry	imidazole	bromoalkyne (R)	product, yield[b]
1		Ph	**1**, 52%
2[c]		TIPS	**2**, 53%
3		*n*-Hex	**3**, 53%
4		$CH_2OTBDMS$	**4**, 22% **16**, 20%
5		$C(CH_3)_2OTBDMS$	**5**, 56%
6		Ph	**6**, 72%
7		TIPS	**7**, 71%
8		*n*-Hex	**8**, 54%
9[c]		Ph	**9a,b**, 71% (9:1)[f]
10		TIPS	**10a**, 90%[c]
11		*n*-Hex	**11a**, 44%[c]
12		Ph	**12**, 28%
13		Ph	**13a,b**, 29% (1:1)[d]
14		TIPS	**14a,b**, 15% (4:1)[d]
15		TIPS	**15a,b**, 79% (9:1)[d]

[a] Except where noted otherwise, all reactions were carried out on a 1 mmol scale in 2 mL of dioxane under argon at 50 °C for 14 h followed by 4 h under reflux. [b] Isolated yields after column chromatography. [c] Reaction carried out at 50 °C overnight. [d] Ratio of 1,4- to 1,5-regioisomeric products **a** and **b**, respectively. [e] None of the 1,5-regioisomeric product was observed.



16 **17**

FIGURE 2. Structures of the *N*-(halovinyl)imidazoles.

regiocontrol could be explained by a combination of steric and electronic effects due to a favorable annular tautomerism.[19]

The coupling reactions of 2- and 4-methylimidazole afforded *N*-alkynylimidazoles as well but in low yield and in the case of 4-methylimidazole with poor regioselectivity (Table 3, entries 12−13). Similarly, the coupling of the challenging 4-(4-fluorophenyl)-5-(4-pyridyl)-1*H*-imidazole[20] affords low yields of a mixture of regioisomeric *N*-alkynylimidazoles (entry 14). In contrast, the related 4-(4-fluorophenyl)imidazole affords the coupling product in good yield and regioselectivity (entry 15).

There are a few observations concerning the proposed mechanism of this coupling reaction. Imidazole and imidazolate are good ligands for both copper(I) and copper(II), and in the case of bridging imidazolate, polymorphic, aggregated complexes are possible.[21] It is noteworthy that the coupling reaction showed little sensitivity to the oxidation state of the copper source used (Table 2, entries 11−14) or the presence or exclusion of air (Supporting Information). Although a catalytically active copper-imidazole species can carry out the coupling in the absence of added ligand (Table 2, entry 8), the efficiency is low, which may arise from catalytically inactive complexes/aggregates. The role of the added ligand may be to promote disaggregation of these imidazole(imidazaolate)/copper complexes and to increase the electron density of the resulting ligand-associated copper complex in order to aid the oxidative addition of the haloalkyne. In this respect, the anionic ligands derived from diketones are strongly electron-donating, so that when they bind to the copper, the oxidative addition reaction is more likely to occur. The increase in coupling yields with increasing reaction temperature that is observed could be partly due to disruption of the copper-imidazole complexes. Solvent polarity could play a similar role; DMSO which enables coupling reaction at room temperature (Table 1, entry 10) is able to bind to the copper[22] and may compete with the ligand imidazole to prevent the aggregation. Finally, the nature of the imidazole partner affects the stability and aggregation state of any complex with copper, which may in part explain why the reactions of 2- and 4-methylimidazole do not work as well as the unsubstituted imidazole (Table 3, entries 12−13).

In conclusion, a copper-catalyzed coupling reaction between imidazoles or benzimidazole and bromoalkynes has been developed to afford *N*-alkynyl derivatives which is both more efficient and of wider scope compared to previous routes to these compounds. This transformation allows access to numerous new *N*-alkynylimidazoles and benzimidazoles, which may display interesting chemical and biological propertires and are potential starting materials in the synthesis of aza-enediyne derivatives.

Experimental Section

General Procedure for the Synthesis of 1-(2-Phenylethynyl)-1*H*-imidazole 1. A reaction flask under argon was charged with Cs_2CO_3 (652 mg, 2 mmol), CuI (10 mg, 0.05 mmol), and imidazole (68 mg, 1 mmol) and backfilled with argon. Dry 1,4-dioxane (2 mL) was added followed by the bromophenylacetylene (0.237 mL, 2 mmol), the 2-acetylcyclohexanone (0.026 mL, 0.2 mmol), and 4 Å molecular sieves (75−115 mg). The mixture was heated to 50 °C in an oil bath for 14 h and then heated to reflux for 4 h. The reaction mixture was cooled to room temperature, quenched with 5 mL of a saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were evaporated and

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subjected to flash chromatography (0−25% EtOAc/hexane) to afford **1** (87 mg, 52% yield) as a white solid: mp 42.1−43.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, s), 7.53−7.48 (2H, m), 7.39−7.34 (3H, m), 7.20 (1H, s), 7.09(1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 131.7 (2C), 129.3, 129.0, 128.5 (2C), 121.7, 121.0, 78.1, 70.3; IR (KBr) 2263, 1478, 1309, 1165, 1067, 1013 cm^{-1}; MS (CI) (*m*/*z*) 337 (2M + 1, 15), 169 (M + 1, 100); HRMS calcd for $C_{11}H_9N_2$ (M + H$^+$) 169.0766, found 169.0769.

1-(*Z*-2-Bromo-1-(*tert*-butyldimethylsilanyloxymethyl)vinyl)-1*H*-imidazole 16. Following the general procedure above (flash chromatography; 0−10% EtOAc/hexane), 47 mg of 1**5** (15%) was obtained as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, s), 7.25 (1H, s), 7.07 (1H, s), 6.52 (1H, t, J = 1.4 Hz), 4.31 (2H, d, J = 1.4 Hz), 0.88 (9H, s), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5 (br), 136.8 (br), 129.3 (br), 118.3 (br), 102.8, 65.1, 25.6 (3C), 18.1, −5.6 (2C); IR (neat) 2954, 2931, 2888, 2857, 1646, 1486, 1382, 1314, 1256, 1140, 1084 cm^{-1}; MS (CI) (*m*/*z*) 635 (2M + 1, 35), 317 (M + 1, 100); HRMS calcd for $C_{12}H_{22}BrN_2OSi$ (M + H$^+$) 317.0685, found 317.0683.

1-(*Z*-2-Chloro-2-phenylvinyl)-4-phenyl-1*H*-imidazole 17. A reaction flask under argon was charged with **9a** (89 mg, 0.36 mmol) and backfilled with argon. DMF (15 mL) was added followed by concd HCl (0.121 mL, approximately 1.46 mmol). The reaction was heated at 80 °C for 3 days and then cooled to room temperature, quenched with a saturated solution of Na_2CO_3, and extracted with CH_2Cl_2. The combined organic layers were subjected to flash chromatography (0−20% EtOAc/hexane) to afford 8 mg of **17** (3%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, s), 7.84−7.79 (2H, m), 7.69−7.65 (2H, m), 7.57 (1H, s), 7.47−7.35 (5H, m), 7.34−7.27 (1H, m), 6.88 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 136.6, 133.0, 132.3, 129.2 (2C), 128.9, 128.7 (2C), 128.6 (2C), 127.5, 125.1 (2C), 123.3, 120.8, 114.1; IR (neat) 2926, 2854, 1718, 1637, 1489, 1446, 1381, 1239, 1184, 1068, 1043, 900 cm^{-1}; MS (CI) (*m*/*z*) 281 (M + 1, 100); HRMS calcd for $C_{17}H_{14}N_2Cl$ (M + H$^+$) 281.0846, found 281.0843.

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Supporting Information Available: General procedure for bromoalkyne preparation, characterization data, and ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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