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# Copper-catalyzed coupling of imidazoles and pyrazoles with 1,1-dibromo-1-alkenes: a distinct approach for direct N-alkynylation of heteroarenes ☆

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ABSTRACT

The direct N-alkynylation of heteroarenes, imidazoles, and pyrazoles with 1,1-dibromo-1-alkene has been carried out for the first time using [Cu(Phen)PPh$_3$Br] (as a catalyst) and $Cs_2CO_3$ in DMSO at 80 °C. The products are formed in good to high yields (66–85%) within 3 h. No side products could be detected.



*N*-Alkynyl heteroarenes exhibit interesting biological[1] and photoconductive properties.[2] They are also useful intermediates in organic synthesis[3] and in medicinal chemistry.[1b] However, the general and mild methods for the synthesis of these compounds are limited and as a consequence these compounds have not been properly explored. The methods reported previously for the synthesis of *N*-alkynyl heteroarenes are multistep procedures involving the coupling of alkynyliodonium salts,[4a] elimination of haloenamines,[4b] and isomerisation of propargyl groups.[4c] Ligand-assisted or ligand-free Cu-catalyzed syntheses of these compounds are also known.[5] However, long reaction times and formation of the side products are the problems. Here, we describe a distinct approach for direct N-alkynylation of heteroarenes applying a Cu (I)-based complex.

In connection with our work[6] on the development of useful synthetic methodologies we have observed that heteroarenes, when treated with 1,1-dibromo-1-alkenes using [Cu(Phen)PPh$_3$Br] (Fig. 1) (as a catalyst) and $Cs_2CO_3$ in DMSO at 80 °C, produced the corresponding *N*-alkylnyl derivatives in 3 h (Scheme 1).

Initially the reaction of benzimidazole (**1a**) with 1,1-dibromo-2-tolyl alkene (**2a**) was thoroughly studied using different copper sources, bases, and solvents (Table 1). Besides the copper source [Cu(Phen)PPh$_3$Br] the following other Cu-complexes (Fig. 1) were

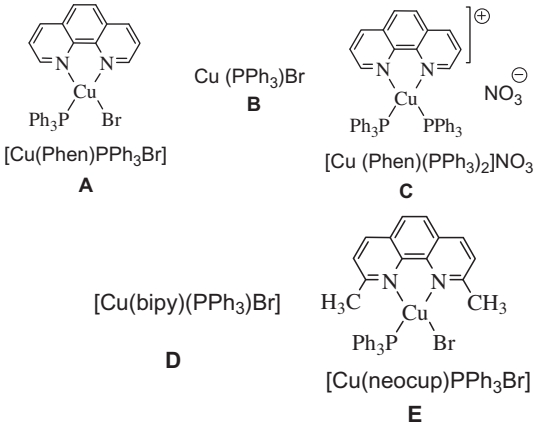


**Figure 1.** Cu-complexes used for N-alkynylation of heteroarenes.

used to catalyze the reaction. The screening studies showed that among all the Cu-sources [Cu(Phen)PPh$_3$Br] (**A**) was most effective in DMSO using $Cs_2CO_3$ as a base (Table 1, entry 8). The conversion was complete in 3 h and the yield of the *N*-alkynyl derivative **3a** was 82%. The reaction was conducted at 80 °C. At room temperature the yield was low even after 12 h. The other Cu-complex **E** was also highly effective—using this catalyst and $Cs_2CO_3$ in DMSO the yield of **3a** was 76% at 80 °C (entry 11).

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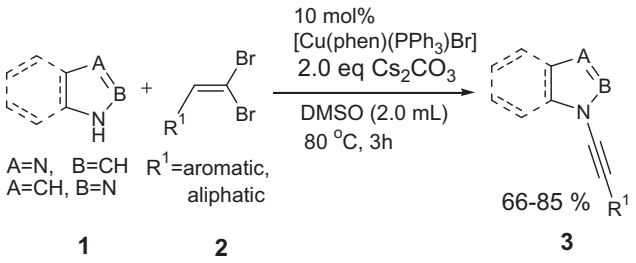



**Scheme 1.** Copper-catalyzed C–N cross coupling.

The catalytic activity of other Cu-sources was not so impressive. CuI and $Cu_2O$ could not catalyze the conversion under ligand-free conditions (entries 13 and 14). Different other bases such as KOH, LiO-*t*-Bu, and $K_3PO_4$ were also used but the yield of **3a** was decreased. Similarly, the other solvents, toluene and 1,4-dioxane diminished the yield. Thus, it was evident that N-alkylnylation of benzimidazole (**1a**) with 1,1-dibromo-2-tolyl alkene (**2a**) took place most efficiently in the presence of [Cu(Phen)$PPh_3$Br] (**A**) as a catalyst using $Cs_2CO_3$ in DMSO at 80 °C and afforded the product **3a** in highest yield in 3 h.

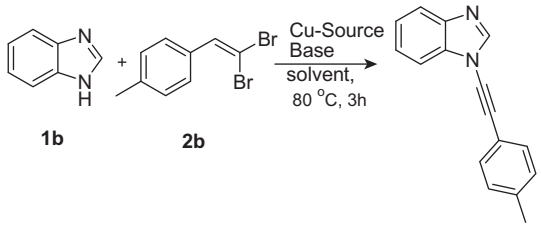
Following the above optimized conditions a series of *N*-alkynylimidazoles (**3**) were prepared. Several substituted imidazoles including benzimidazole were applied. The imidazoles contained alkyl groups as well as aryl groups as substituents at different positions. Both aromatic and aliphatic *gem*-dibromo alkenes were used. These compounds were conveniently prepared from the corresponding aldehydes by treatment with $CBr_4$.[7] 1,1-Dibromo 2-(1-naphthyl) ethylene was also applied for N-alkynylation. The yields of *N*-alkynyl imidazoles were high (66–85%). No side product was observed and only the starting heteroarenes were recovered.

When an amide such as benzamide was treated with 1,1-dibromo 2-phenyl ethylene under the present conditions amide did not involve in the reaction and remained unchanged. However, alkene underwent homocoupling[8] to produce 1,3-diyne (1,4-diphenyl but-1,3-diyne) in good yield (67%).

The above N-alkynylation reaction of imidazoles was also successfully applied to pyrazoles (Table 2, entries 3n, 3o). The reaction was complete in 3 h and the corresponding *N*-alkynyl derivatives were formed in high yields (68–69%). In each reaction only a single derivative was formed. The structures of the products were established from their spectral (IR, $^1H$ and $^{13}C$ NMR, and ESIMS) data.

The catalyst, [Cu(Phen)$PPh_3$Br] (**A**) can easily be prepared[9] by the addition of 1,10-phenantholine to a solution of tris-(triphenyl phosphine) copper(I) bromide in $CHCl_3$ at room temperature. The complex is stable in air and soluble in DMSO. It is also economically favorable compared to the complexes derived from noble metals.

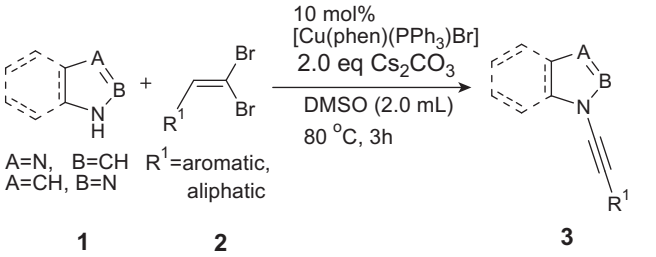
**Table 1**
Screening of Cu(I)-sources, solvents and bases for N-alkynylation of heteroarenes[a]

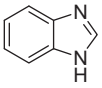
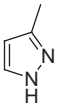



| S. No | Cu(I)-source | Base | Solvent | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Cu($PPh_3$)$_3$Br | $Cs_2CO_3$ | Toluene | 61 |
| 2 | [Cu(Phen)$PPh_3$Br] | $Cs_2CO_3$ | 1,4-Dioxane | 67 |
| 3 | [Cu(Phen)$PPh_3$Br] | KOH | 1,4-Dioxane | 53 |
| 4 | [Cu(Phen)($PPh_3$)$_2$]$NO_3$ | $Cs_2CO_3$ | DMSO | 63 |
| 5 | [Cu(bipy)$PPh_3$Br] | $Cs_2CO_3$ | 1,4-Dioxane | 64 |
| 6 | [Cu(bipy)$PPh_3$Br] | LiO-*t*-Bu | 1,4-Dioxane | 68 |
| 7 | [Cu(bipy)$PPh_3$Br] | $K_3PO_4$ | DMSO | 57 |
| 8 | [Cu(Phen)$PPh_3$Br] | $Cs_2CO_3$ | DMSO | 82 |
| 9 | [Cu(Phen)$PPh_3$Br] | LiO-*t*-Bu | DMSO | 72 |
| 10 | [Cu(Phen)$PPh_3$Br] | $K_3PO_4$ | DMSO | 69 |
| 11 | [Cu(neocup)$PPh_3$Br] | $Cs_2CO_3$ | DMSO | 76 |
| 12 | [Cu(neocup)$PPh_3$Br] | KOH | DMSO | 66 |
| 13 | CuI | $Cs_2CO_3$ | DMSO | 0[c] |
| 14 | $Cu_2O$ | $Cs_2CO_3$ | DMSO | 0[c] |
| 15 | CuI/DMEDA | $Cs_2CO_3$ | DMSO | 64 |

[a] Reaction conditions: Benzimidazole (1.0 mmol), 1,1-dibromo-2-tolyl-alkene (1.2 mmol), Cu source (10 mol %), 2.0 equiv of base, 2.0 mL of solvent at 80 °C for 3 h.
[b] Isolated yield after column chromatography.
[c] Homocoupling of 1,1-dibromo-2-tolyl-alkene and 1,3-diyne was formed.

**Table 2**
Cu(I) catalyzed N-alkynylation of heteroarenes[a,b]




| S. No | Imidazole/pyrazole (**1**) | $R^1$ (**2**) | Product (**3**) | Yield[c] (%) |
|---|---|---|---|---|
| a |  | $C_6H_5$ | **3a** | 78 |
| b | | 4Me-$C_6H_4$ | **3b** | 82 |
| c | | 4Cl-$C_6H_4$ | **3c** | 85 |
| d | | 4F-$C_6H_4$ | **3d** | 76 |
| e | | $CH_3(CH_2)_5CH_2$ | **3e** | 75 |
| f |  | $C_6H_5$ | **3f** | 66 |
| g |  | $C_6H_5$ | **3g** | 69 |
| h |  | $C_6H_5$ | **3h** | 78 |
| i | | 4Me-$C_6H_4$ | **3i** | 84 |
| j |  | $C_6H_5$ | **3j** | 71 |
| k |  | 1-Naphthyl | **3k** | 74 |
| l |  | 4Cl-$C_6H_4$ | **3l** | 81 |
| m | | $CH_3(CH_2)_4CH_2$ | **3m** | 72 |
| n |  | $C_6H_5$ | **3n** | 69 |
| o |  | $C_6H_5$ | **3o** | 68 |

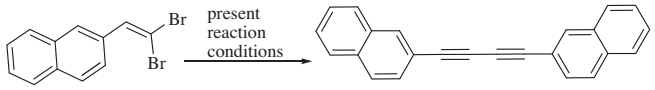
[a] Reaction conditions: Imidazole or pyrazole (1.0 mmol), 1,1-dibromo-2-aryl-alkene (1.2 mmol), [Cu(Phen)$PPh_3$Br] (10 mol %), 2.0 equiv of $Cs_2CO_3$, 2.0 mL of DMSO at 80 °C for 3 h.
[b] Compounds **3b, 3c, 3d, 3e, 3i, 3k, 3l, 3m** are unknown.
[c] Isolated yield after chromatography.

A plausible mechanism[10] of the present conversion using this catalyst is shown in Scheme 2. The mechanism involves the (heteroaryl) Cu(I) intermediate **I** and the Cu(III) complex **II** to yield the *N*-alkynyl derivative **3**.

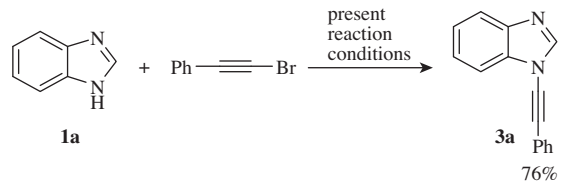
In another probable mechanism alkynyl bromides derived from 1,1-dibromo-1-alkenes interact with **I** to form the complex **IV** which subsequently produces the alkynylated derivative **3** (Scheme 3).

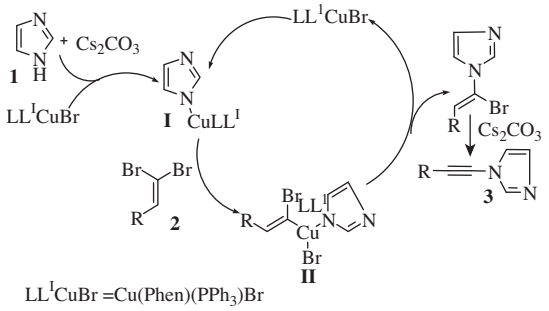
The present conversion took place spontaneously and we were not able to isolate any intermediate. However, to get an idea about the mechanism of the conversion we carried out two reactions which are mentioned below.

(i) Only 1,1-dibromo-1-alkene (without using an heterocycle) was applied[8] for the conversion under the present reaction conditions.

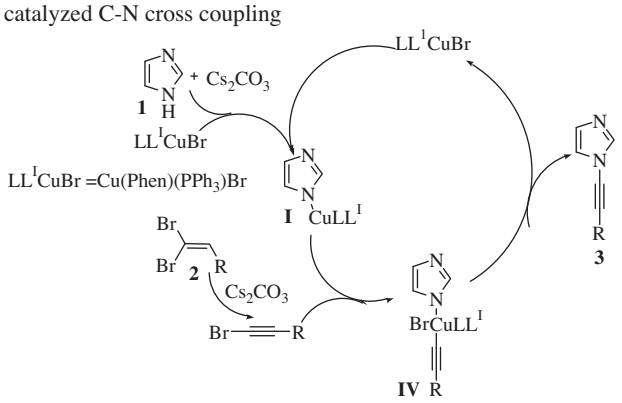



(ii) An imidazole was treated[5c] with bromoacetylene under the present reaction conditions.




**Scheme 2.** Probable mechanism of the copper-catalyzed C–N cross coupling.




**Scheme 3.** An alternative probable mechanism of the copper-catalyzed C–N cross coupling.

Though it is reported[11] in some cases that alkynyl bromides (derived from the *gem*-dibromo alkenes by dehydrobromination) require strong bases and higher temperature, we feel under the conditions mentioned here the second mechanism (Scheme 3) is more favorable for the present conversion leading to the alkynylated products.[5c]

In conclusion we have developed for the first time an efficient method[12] for direct N-alkynylation of heteroarenes with 1,1-dibromo 1-alkene using [Cu(Phen)$PPh_3$Br] as a cost-effective catalyst.

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12. *General experimental procedure for N-alkynylation of imidazole and pyrazole derivatives*: To a solution of 1,1 dibromo alkene **2** (1.0 mmol) in DMSO (2 mL) imidazole (or) pyrazole **1** (1.5 mmol), $Cs_2CO_3$ (2.0 equiv), and [Cu(Phen)($PPh_3$)Br] (10 mol %) were added. The mixture was heated on an oil bath at 80 °C for 3 h. The reaction was monitored by TLC. Upon completion, the mixture was cooled to room temperature and cold $H_2O$ (10 mL) was added to the residue. The mixture was extracted with EtOAc (2 × 10 mL). The organic layers were dried (anhydrous $Na_2SO_4$) and concentrated in vacuo. The viscous mass was purified by column chromatography (silica gel, Merck 60–120 mesh, 1–4% EtOAc–hexane) to afford the pure product (**3**). The unreacted heteroarene was also recovered.
The spectral data of the unknown products.
Compound **3b**. White solid. Mp 83–84 °C; IR: 2255, 1606, 1489, 1452, 1283 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.10 (1H, s), 7.81 (1H, d, $J$ = 8.0 Hz), 7.62 (1H, d, $J$ = 8.0 Hz), 7.43 (2H, d, $J$ = 8.0 Hz), 7.33 (2H, d, $J$ = 8.0 Hz), 7.19 (2H, d, $J$ = 8.0 Hz), 2.41 (3H, s); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 143.8, 142.2, 139.5, 134.6, 132.0, 129.3, 124.8, 124.1, 121.0, 118.2, 111.1, 75.9, 73.8, 21.5; ESIMS: $m/z$ 233 $[M+H]^+$; Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.68; H, 5.27; N, 12.10.
Compound **3c**. Brown solid. Mp 81–83 °C; IR: 2258, 1605, 1490, 1455, 1239 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.11 (1H, s), 7.82 (1H, d, $J$ = 8.0 Hz), 7.62 (1H, d, $J$ = 8.0 Hz), 7.49 (2H, d, $J$ = 8.0 Hz), 7.42–7.31 (4H, m); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 143.6, 142.2, 135.1, 134.4, 133.0, 129.0, 125.1, 124.2, 121.0, 119.9, 110.8, 73.0, 70.1; ESIMS: $m/z$ 253, 255 $[M+H]^+$; Anal. Calcd for $C_{15}H_9N_2Cl$: C, 71.29; H, 3.59; N, 11.09. Found: C, 71.34; H, 3.52; N, 11.12.
Compound **3d.** Yellow solid. Mp 86–87 °C; IR: 2254, 1599, 1492, 1459, 1230 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.14 (1H, s), 7.84 (1H, d, $J$ = 8.0 Hz), 7.63 (1H, d, $J$ = 8.0 Hz), 7.59–7.52 (2H, m), 7.48–7.32 (2H, m), 7.17–7.05 (2H, m); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 163.1 (d, $J$ = 280.0 Hz), 143.9, 141.9, 133.8, 133.7, 124.9, 124.0, 120.9, 117.2, 115.8 (d, $J$ = 10.0 Hz), 110.9, 76.1, 72.2; ESIMS: $m/z$ 237 $[M+H]^+$; Anal. Calcd for $C_{15}H_9N_2F$: C, 76.26; H, 3.84; N, 11.86. Found: C, 76.29; H, 3.78; N, 11.79.
Compound **3e.** Yellow oil; IR: 2270, 1613, 1496, 1460, 1225 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.98 (1H, s), 7.75 (1H, d, $J$ = 8.0 Hz), 7.50 (1H, d, $J$ = 8.0 Hz),

7.35–7.23 (2H, m), 2.43 (2H, t, $J$ = 7.0 Hz), 1.69–1.61 (2H, m), 1.51–1.42 (2H, m), 1.39–1.22 (6H, m), 0.98 (3H, t, $J$ = 7.0 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 144.0, 142.2, 135.1, 124.5, 123.9, 121.0, 110.9, 73.3, 68.8, 31.9, 29.0, 28.9, 28.8, 22.9, 18.8, 14.2; ESIMS: $m/z$ 241 $[M+H]^+$; Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 79.89; H, 8.47; N, 11.73.

Compound **3i.** Brown oil; IR: 2257, 1498, 1428, 1376, 1256 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.34 (2H, d, $J$ = 8.0 Hz), 7.13 (2H, d, $J$ = 8.0 Hz), 7.02 (1H, br s), 6.88 (1H, br s), 3.29 (1H, m), 2.39 (3H, s), 1.40 (6H, d, $J$ = 7.0 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 143.4, 134.4, 130.5, 129.2, 128.3, 127.1, 121.2, 78.1, 72.6, 27.0, 21.5, 20.8; ESIMS: $m/z$ 225 $[M+H]^+$; Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.27; H, 7.15; N, 12.54.

Compound **3k.** Brown oil; IR: 2254, 1506, 1473, 1434, 1384, 1287 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.20–8.10 (3H, m), 7.83 (2H, t, $J$ = 8.0 Hz), 7.66 (1H, d, $J$ = 8.0 Hz), 7.52–7.40 (6H, m), 7.38 (1H, br s), 7.17 (1H, br s); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 138.2, 135.9, 133.1, 130.5, 129.9, 129.1, 129.0, 128.7, 128.3, 127.1, 126.3, 126.2, 125.5, 125.1, 123.8, 122.2, 70.9, 69.6; ESIMS: m/z 295 $[M+H]^+$; Anal. Calcd for $C_{21}H_{14}N_2$: C, 85.69; H, 4.79; N, 9.52. Found: C, 85.73; H, 4.81; N, 9.56.

Compound **3l.** Yellow solid. Mp 182–184 °C; IR: 2259, 1593, 1482, 1411, 1145 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.81 (1H, s), 7.72 (2H, d, $J$ = 8.0 Hz), 7.48–7.32 (7H, m), 7.23 (1H, t, $J$ = 8.0 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 142.3, 140.1, 135.2, 132.8, 132.7, 129.1, 128.9, 127.9, 125.2, 119.8, 116.8, 78.9, 70.0; ESIMS: $m/z$ 279, 281 $[M+H]^+$; ESIMS: $m/z$ 295 $[M+H]^+$; Anal. Calcd for $C_{17}H_{11}N_2Cl$: C, 73.25; H, 3.98; N, 10.05. Found: C, 73.21; H, 3.93; N, 10.09.