Copper-in-Charcoal-Catalyzed, Tandem One-Pot Diazo Transfer-Click Reactions

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Abstract: Copper-in-charcoal (Cu/C) is an effective heterogeneous catalyst for tandem diazo transfer/ click reactions. In the presence of Cu/C, various azides can be generated in situ from the corresponding amines, and subsequently undergo [3+2] cycloaddition with terminal alkynes to afford triazoles in good yields. The catalyst is also easily recycled.

Keywords: click chemistry; copper-in-charcoal; diazo transfer; heterogeneous catalysis

Both the Sharpless^[1] and Meldal^[2] groups are credited with describing the remarkable acceleration induced by Cu(I) in Huisgen [3+2] cycloadditions^[3] between azides and terminal alkynes. Such cycloaddition reactions are among the most popular protocols for generating libraries of compounds in drug research,^[4] materials science,^[5] and bioconjugate chemistry.^[6] Cu(I)catalyzed azide-alkyne cycloadditions (CuAAC) have been extensively investigated leading to several modified procedures for purposes of simplifying both educt and reagent manipulation.^[7] Recently, Wittmann^[8] and co-workers reported a one-pot procedure leading to 1,4-disubstituted 1,2,3-triazoles from in situ-generated azides, by-passing safety issues associated with the handling of these potentially explosive compounds.^[9] However, after Cu(II)-induced azide formation, introduction of a reducing agent (sodium ascorbate or copper powder) is required to convert Cu(II) to click-active Cu(I).

The need for both oxidation states of copper suggested that our previously^[10] reported reagent, copper-in-charcoal (Cu/C), might serve as an efficient *heterogeneous* catalyst for these tandem processes. XPS spectral data for Cu/C reveal the presence of mostly CuO, along with lesser amounts of Cu₂O in the charcoal matrix, seemingly ideal for an initial diazo transfer and subsequent [3+2] cycloaddition. In this report we describe an especially convenient, one-pot procedure employing a heterogeneous, recyclable, and soon-to-be-commercially available reagent (Cu/C)^[11] for catalysis that sequentially converts primary amines to 1,4-disubstituted 1,2,3-triazoles without adding reducing reagents (Scheme 1).



Scheme 1. Cu/C-catalyzed tandem reactions.

Azides were readily prepared *in situ* from the corresponding amines *via* diazo transfer mediated by trifluoromethanesulfonyl azide **1** (TfN₃; Scheme 2). Reagent **1** was made from the reaction of trifluoromethanesulfonyl anhydride and sodium azide in a mixture of water and dichloromethane (DCM) at $0^{\circ}C$.^[12] For reasons of safety, azide **1** is handled in DCM, which is separated from the aqueous phase and used directly. Benzylamine **2** and phenylacetylene (**3**) were



Scheme 2. Two steps, one-pot procedure.

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chosen as a model substrate pair to test efficacy of Cu/C. The former was transformed into benzyl azide in the presence of Cu/C following Wong's procedure^[12] wherein sodium bicarbonate serves as base. However, under these conditions, leaching of copper(II) from the charcoal matrix was noticeable as revealed by the blue coloration of the solution. Presumably, breakup of polymeric copper oxides to form copper carbonate within the charcoal pores may be the release mechanism. By simply switching to barium hydroxide, active copper remains on the solid support. Once diazo transfer is complete (monitored by GC; diazo transfer stopped at 80% conversion after 3 h), phenylacetylene and triethylamine^[10] were

added. After 18 h of stirring at room temperature, the desired triazole was obtained in 95% isolated yield. Use of Cu/C prepared by Sigma–Aldrich led to the same results under identical conditions (entry 1; Table 1).

The scope of this methodology has been studied using a variety of amines and alkynes, as illustrated in Table 1. Aromatic and aliphatic primary amines can be smoothly transformed to their corresponding azides. In all cases, triazole products were isolated in good-to-excellent yields. It appeared that sterically hindered alkynes (entries 2 and 4), and an alkyne with a long carbon chain (entry 6), displayed lower reactivity and thereby prolonged reaction times were

Table 1. Representative examples of Cu/C-catalyzed tandem azide formation/click reaction.^[a]

		Cu/C, Ba(OH) ₂			Cu/C, TEA	
	K^-NH_2 + TIN_3^{IV}	DMC	-	rt in ₃	R' DMC	Ń≈ <mark>N</mark> ~R
Entry	Amine	Alkyne	T [°C]	Time [ł	n] Triazole	Yield [%] ^[c]
1		Ph	rt	18	Ph N Ph	95 (96) ^[d]
2	Ph NH ₂	OH	40	40		88 ^[d]
3	MeO CI		40	18	MeO N	92
		но //	40	18	N-N	45
4	NH ₂	\bigvee	40	48		99
5	MeO OMe	1-octyne	40	18	MeO MeO N=N	91(86) ^[e]
	NH ₂	2	40	18	MeO、	35
6	MeO OMe	1-dodecyne	40	48		4) 99 9
7	Ph NH ₂	TIPSO	40	18		97 IPS
8	O N NH ₂	N	40	18		9 1
9	Ph NH ₂	TBSO	40	24	Ph N N N OTBS	72

^[a] Standard conditions: Cu/C (12 mol%), Ba(OH)₂ (1.5 mmol), TfN₃ (1.5 mmol), amine (1.5 mmol), alkyne (0.75 mmol), TEA (1.4 mmol).

- ^[d] Sigma–Aldrich Cu/C was used.
- ^[e] Recovered Cu/C was used.

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^[b] TfN₃ was prepared prior to use.

^[c] Isolated yields.

required. It is worthy of note that high-molecularweight adduct **4** could also be formed and isolated in good yield (Figure 1).





A significant advantage of this heterogeneous catalyst is its recyclability without loss of activity (Table 1, entry 5). The recovered Cu/C gave the desired product in 86% yield under identical conditions as compared to 91% yield using fresh reagent.

The influence of microwave irradiation was examined in an effort to enhance the rate of the click step; cycloaddition of phenylacetylene (3) with *in situ*-generated benzyl azide was complete in 10 min at 120 °C, giving the product in 92% isolated yield (Scheme 3).



Scheme 3. Microwave-assisted click reaction.

To confirm that this one-pot procedure catalyzed by Cu/C is unambiguously heterogeneous in nature, azide **5** was generated *in situ* followed by addition of Cu/C, alkyne **6**, and triethylamine (Scheme 4). The mixture was stirred for four hours at 40 °C and then analyzed by GC: the ratio of educt **6** to product was 79:21. The incomplete reaction mixture was then filtered to remove Cu/C and the filtrate subjected to the same 40 °C for another 16 h. That the ratio did not change strongly suggests that no copper was present in solution. Introduction of fresh Cu/C to the filtrate led to full conversion of the reaction. Although these observations do not rule out the possibility that Cu/C is serving as a reservoir of copper in solution that returns to the solid support, the lack of any coloration (as previously seen; *vide supra*) and the mildness of reaction conditions (room temperature to 40 °C) argue against such a role for this catalyst.

In conclusion, a heterogeneous, one-pot procedure for sequential Cu(II)-catalyzed diazo transfer of amines to azides followed by Cu(I)-catalyzed click cycloaddition between resulting azides and alkynes has been developed. Both the isolation of azide intermediates and introduction of reducing agents are obviated using readily available, heterogeneous Cu/C.

Experimental Section

General Procedure for Cu/C-Catalyzed, One-Pot "Click" Reaction

A solution of NaN₃ (200 mg, 3.0 mmol) in a mixture of H₂O (1 mL) and CH₂Cl₂ (1 mL) was cooled at 0°C and treated with Tf₂O (250 µL, 1.5 mmol) while stirring. The reaction mixture was stirred in an ice-bath for 2 h. The organic phase was then separated and the aqueous phase was extracted twice with CH₂Cl₂. The organic layers were combined and washed (~3 mL) with saturated Na2CO3 (5 mL) and used without further purification. A 25-mL round-bottomed flask was charged with Cu/C (50 mg, 1.83 mmol g^{-1} , 0.09 mmol), $Ba(OH)_2$ (256 mg, 1.5 mmol), amine (1.5 mmol), and CH₂Cl₂ (2 mL). While the mixture was stirred at room temperature, a fresh solution of TfN3 in CH2Cl2 was added slowly. After 3 h stirring at room temperature, triethylamine (200 µL, 1.4 mmol) and alkyne (0.75 mmol) were added. The resulting mixture was heated to the temperature indicated in Table 1. Upon complete consumption of alkyne as monitored by TLC, Cu/C was removed by filtration on a Buchner funnel charged with a short pad of Celite and the filter cake was washed with 10 mL of DCM. The filtrate was collected and concentrated via rotary evaporator and purified via flash chromatography. Compound characterization data are available in the Supporting Information.

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