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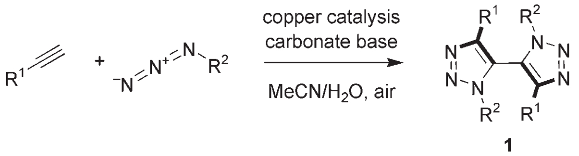
Click Chemistry

Base Dependence in Copper-Catalyzed Huisgen Reactions: Efficient Formation of Bistriazoles**

*Yu Angell and Kevin Burgess**

Copper-accelerated[1,2] Huisgen additions[3,4] of azides to alkynes are archetypical examples of "click chemistry".[5] These were originally reported by Meldal and co-workers.[1]Since then Sharpless and co-workers recognized their privileged status: the reactions take place with high yields, under mild conditions, and use copper sources that have no impact on most other functional groups.[2] These reactions are undeniably useful in contemporary organic chemistry.[6]

In our research group, we often observed a minor impurity by analytical HPLC when we prepared libraries of triazoles through these copper-mediated reactions. LC-MS analyses indicated these were oxidative dimers of the desired product (that is, $[2M^{+}-2H]$). Sharpless and co-workers previously noticed such minor amounts of by-products and, without reporting their characterization, they attributed these by-products to the direct use of Cu^{I} species.[2] However, we observed significant amounts of these products when we attempted azide–alkyne coupling reactions of crude substrates, even with a $CuSO_4$/Cu powder system. Here we report that these oxidative dimers have the structure **1** and that they can be the major products under basic conditions [Eq. (1)].

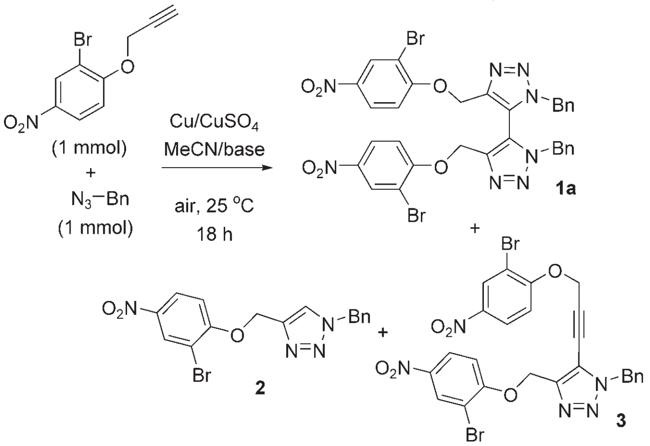


(1)

1
major product

We varied the reaction conditions in an attempt to optimize the yield of compound **1a** in this Cu-mediated process, but most attempts were unsuccessful (see the Supporting Information). For example, triazole **2** (Table 1) was the main product when the reaction was performed under nitrogen with $Cu/CuSO_4$, but the catalyst was rapidly deactivated and the starting materials remained when the reaction was performed under pure oxygen. Attempts were made to increase the amounts of the oxidative dimer by addition of palladium catalysts, but these had little effect. Finally, the base was identified as the key variable. The model transformation in Table 1 was chosen because the oxidative-dimerization product **1a** was fully characterized at an early stage in the work. Compound **1a** was a by-product in the presence of 1.5 M $NaHCO_3$, but was the major product when K_2CO_3 was used. The optimal base concentration was found to be 1–2 M; at higher concentrations the alkyne **3** became more prevalent.

Table 1: Effects of bases on the oxidative dimerization process.[a]



Entry	Base	Conc. of base [M]	Product distribution [%][b] 1a	2	3
1	$NaHCO_3$	1.5	12	88	0
2	K_2CO_3	1.5	95	2	3
3	K_2CO_3	2.0	93	3	4
4	K_2CO_3	4.0	84	2	13
5	Na_2CO_3	2.0	95	3	2
6	$(NH_4)_2CO_3$	2.0	0	100	0
7	LiOH	1.5	33	57	10
8	KOH	5.0	50	0	50
9	K_3PO_4	4.0	56	38	6

[a] Reactions carried out with Cu powder (1.0 equiv), $CuSO_4$ (0.1 equiv) in a 1:1 mixture of MeCN/aqueous base (3 mL) in air at 25 °C for 18 h; Bn = benzyl. [b] Determined by analytical HPLC on a C18 column (MeCN, H_2O).

Ammonium carbonate (Table 1, entry 6) gave only the standard click product **2**, which implies that Cu–NH_3 coordination prevents oxidative dimerization. Hydroxide or phosphate bases gave mixed results (Table 1, entries 7–9), which could mean that the ligation of the carbonate ion to the copper center assists in the formation of the oxidative dimer.

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[*] Y. Angell, Dr. K. Burgess
Department of Chemistry
Texas A&M University
PO Box 30012, College Station, TX 77842-3012 (USA)
Fax: (+1) 979-845-8839
E-mail: burgess@tamu.edu

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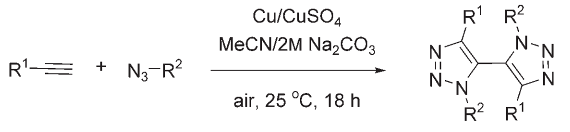
Other experiments with K_2CO_3 additive indicated that the oxidative dimerization was more prevalent in 1:1 $MeCN/H_2O$ than THF/H_2O or $MeOH/H_2O$ mixtures, but the differences were relatively small. The extent of oxidative dimerization was lower when an inert atmosphere was used, but under pure oxygen the reaction gave mostly starting materials.

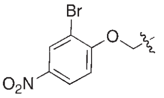
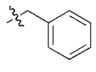
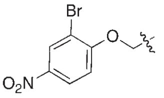
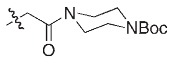
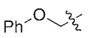
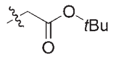
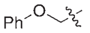
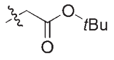
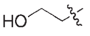
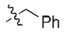
Various control experiments were performed to elucidate the origin of the oxidative dimer **1a**. When the triazole **2** was isolated and then exposed to the conditions in entry 2 (Table 1), we observed no formation of **1a**. Similarly, when compound **3** was mixed with benzyl azide and then subjected to the identical reaction conditions, we again detected no oxidative dimer **1a**. Compounds **2** and **3** are therefore not intermediates in the formation of the oxidative dimer **1a**.

Table 2 shows examples in which the oxidative dimerization methodology was extrapolated to other substrates. In all cases the products **1** were separated conveniently from the other materials by using simple flash chromatography. Compounds **1a–d** all have propargylic oxygen atoms and were isolated in higher yields compared with compounds **1e–g**. The oxidative dimerization reaction did not work when the reactants were hindered and in such cases the triazole **2** was formed; however, longer reaction times were required compared with reactions under neutral conditions (data not shown).

Table 2: Syntheses of bistriazole product **1**.[a]

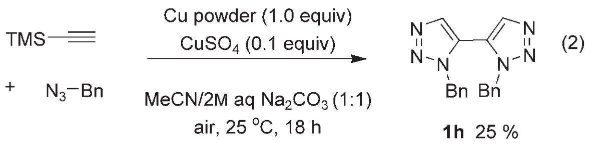


1

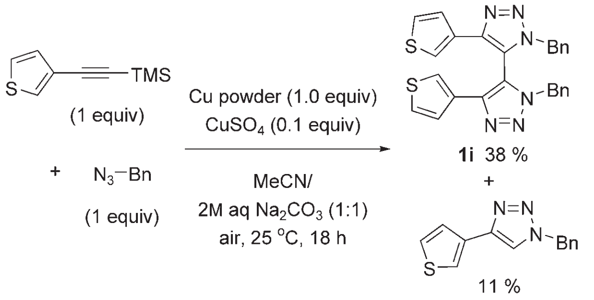
Cmpd	R^1	R^2	Yield [%][b]
1a			87
1b			72
1c			47
1d			69
1e			37
1f			23
1g			34

[a] Reactions carried out with Cu powder (1.0 equiv), $CuSO_4$ (0.1 equiv) in a 1:1 mixture of MeCN/2 M aq Na_2CO_3 in air at 25 °C for 18 h; Boc = *tert*-butoxycarbonyl. [b] Yield of isolated product.

The Sonogashira reaction[7] of trimethylsilylethyne (TMS−C≡CH) followed by desilylation is the most commonly used method to access alkyne starting materials for Cu-mediated cycloaddition reactions. However, if the oxidative dimerization products **1** are desired, we considered that the basic conditions of the reaction might facilitate the deprotection of 1-trimethylsilyl alkynes in situ, thus saving a step. Equations (2) and (3) show how this idea was validated.



(2)



(3)

The reaction shown in Equation (4) is interesting because it highlights the fact that the core of the bistriazole unit is chiral. The bistriazole core of **1** has not previously been reported with this substitution pattern (although regioisomeric materials have been made).[8] Figure 1 shows a molecular representation from a single-crystal X-ray analysis of compound **1e**. Rotation around the C−C bond that connects the two rings is highly hindered; hence the 5,5′-bistriazole is chiral and the enantiomeric forms do not interconvert under ambient conditions. Consistent with this, the AB-quartet pattern observed for the benzylic protons of compound **1e** in the ^{1}H NMR spectrum at ambient temperature do not coalesce into a singlet signal when the sample is heated to 115 °C in dimethyl sulfoxide. In the particular case of

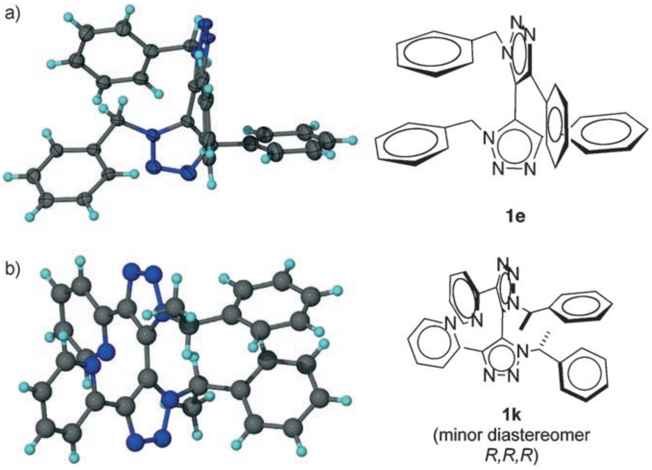
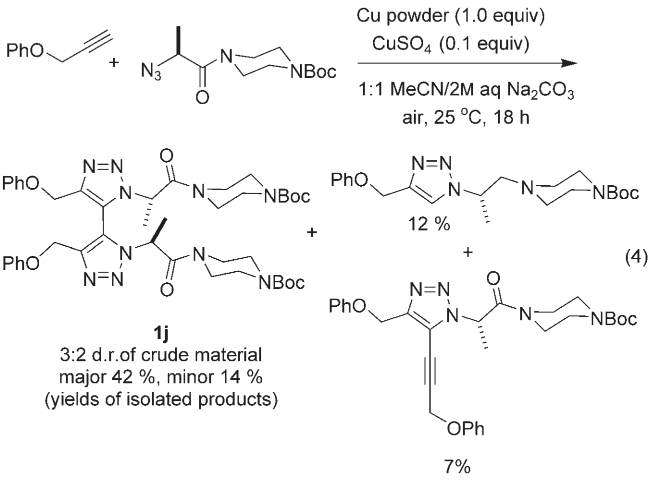
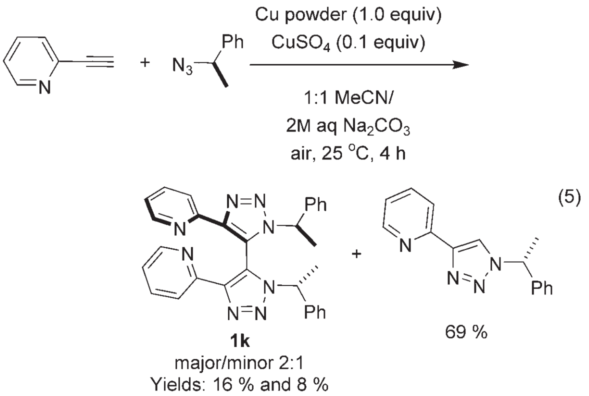


Figure 1. Representations from single-crystal X-ray analysis of: a) **1e** and b) **1k**, which show the stereochemistry of the atropisomeric chiral center in the minor diastereomer of the bistriazole.

compound **1j**, the peripheral chiral center gave two diastereomers with some selectivity (ratios determined by NMR spectroscopy throughout). Furthermore, the diastereomers proved separable by column chromatography.

Production of optically active 5,5′-bistriazoles is expected to be of most interest for the synthesis of new chiral ligands and auxiliaries. In such compounds the heterocyclic core is a stereoelectronic and patentable modification of chiral biaryl cores, which are frequently encountered in ligands.[9] The reaction shown in Equation (4) was performed to explore this concept, and although the diastereoselectivity achieved was unexceptional, the products were easily separated by flash chromatography, so the approach is extremely practical. The atropisomeric stereochemistry of the chiral bipyridyl product [Eq. (5)] (minor product) was proven by using single-crystal X-ray analysis.





The fact that compounds **2** and **3** (Table 1) do not react to form the 5,5′-bistriazole **1a** rules out these compounds as intermediates for the reaction and the possible involvement of diynes. It seems highly likely that the reaction therefore proceeds through the coupling of two organocopper species. Use of sodium or potassium carbonate as the base was found to be favorable for the dimerization process. It could be that carbonate-bridged copper dimers are particularly well suited, and these do not form efficiently from sodium bicarbonate (Table 1, entry 1). Ammonia produced from the use of ammonium bicarbonate may inhibit the formation of this carbonate complex or its mode of action (Table 1, entry 6). Dicopper species have been implicated in copper-mediated additions of azides to alkynes,[2,10] and carbonate-bridged dicopper complexes are well known.[11–13] A plausible mechanism for the reaction therefore features two σ-bonded triazole units that come together in an oxidative coupling reaction, for which carbonate is a particularly favorable bridging ligand. However, we have no direct evidence to implicate dicopper species or the bridging carbonate ligand at this time.

In summary, oxidative coupling can be the prevalent pathway in copper-mediated Huisgen reactions of azides and terminal alkynes, which is surprising because it has been stated several times that the pH value is relatively unimportant for copper-mediated cycloadditions to give triazoles.[2,10] 5,5′-Bistriazoles are an under-explored heterocyclic backbone. However, the reactions described here allow ready access to these compounds and should provide a foundation for further studies. In particular, use of optically active constituents provides a way to make and isolate diastereomerically pure derivatives that represent different atropisomeric forms. Overall, these findings may have an impact on the synthesis of ligands and the development of libraries to screen for pharmaceutical lead compounds; it should influence the strategies used to design conditions for the formation of triazole or bistriazole products.

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Keywords: alkynes · azides · copper · heterocycles · homogeneous catalysis

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