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Base and concentration effects on the product distribution in copper-promoted alkyne–azide cycloaddition: additive-free route to 5-iodo-triazoles

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ABSTRACT

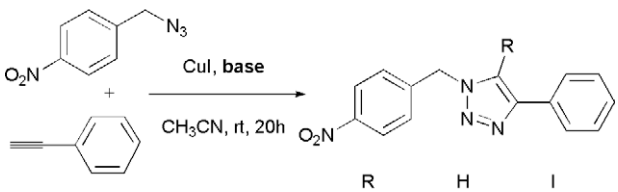
Formation of 5-iodo-triazoles in CuI-promoted cycloadditions between alkynes and azides is controlled by DMAP and low alkyne concentrations.

Copper-promoted alkyne–azide cycloaddition, routinely called 'click-chemistry', has become one of the premier synthetic tools that has found numerous applications.[1] From the synthetic point of view, these cycloadditions are characterized by high yields, mild conditions, and high tolerance to many functional groups.[1] In the case of CuI-promoted alkyne-azide cycloadditions, the presence of a base is required to facilitate the formation of copper acetylides, which are the active species for the reaction with the azides.[2] In general, i-Pr_2EtN (Hünig's base) or Et_3N has been the bases of choice for reactions conducted under non-aqueous conditions, while furnishing 1,4-disubstituted 1,2,3-triazoles as major or exclusive cycloaddition products.[3] Although the effect of organic bases on this cycloaddition reaction is generally believed to have no significant impact on the product distribution,[4] there are several accounts demonstrating that additives might have a profound effect on the outcome of this reaction.[5]

During the course of some of our studies on copper-promoted alkyne-azide cycloadditions, we observed that when Hünig's base was substituted with 4-dimethylaminopyridine (DMAP), a formation of ca. 20% of 5-iodo-1,4-triazole was noted (Scheme 1).[6] Although iodo-containing triazoles are sometimes reported as minor products in various copper-catalyzed and copper-promoted alkyne–azide cycloadditions,[7] there are no reports, to our knowledge, on the ability of DMAP (or any other organic base) to control the product distribution in the alkyne-azide cycloadditions.[8] 5-Iodo-triazoles are valuable synthons for a variety of cross-coupling reactions.[9] In addition, interactions featuring C-Hal compounds are important in modulating various recognition processes relevant to supramolecular and biological processes,[10] which further increases the value of 5-iodo-triazoles. The incorporation of iodine onto the triazole moiety usually requires the presence of electrophilic iodine (I^+) to produce 5-iodo-triazoles.[11] Hence, the formation of the iodo-triazoles by simply switching the base, that is, from *i*-Pr_2EtN to DMAP, presents an unexplored and interesting paradigm.

Herein, we wish to report on a base-controlled CuI-promoted alkyne–azide cycloaddition. We started by screening a range of conditions, including common aromatic bases that are structurally related to DMAP, such as pyridine and *N*,*N*-dimethylaniline (DMA) (Table 1).[12]

Surprisingly, in DMAP-promoted reactions, the formation of the iodo-trizole correlated with the alkyne concentration. Lowering alkyne concentration (from 1.0 M to 3.5 mM) yielded 5-*I*-triazole **2** as the major cycloaddition product (Table 1, entries 1–3). One of the possible sources for the formation of 5-*I*-triazoles is the iodination of 5-*H*-triazole, although non-electrophilic nature of iodine in CuI makes this scenario unlikely. Nonetheless, we investigated the distribution between **1** and **2** as a function of time. The ratio of these triazoles was found to be time independent at both 1.0 M and 3.5 mM concentrations of the alkyne, while using equimolar amounts of azide, DMAP, and CuI. At 3.5 mM, no 5-*H*-triazole was detected at any given time point. Also, when **1** was treated with an equimolar mixture of DMAP and CuI for 20 h, 5-*I*-triazole **2** was not detected, and **1** was recovered unchanged. Hence, it is



R	H	I
iPr2EtN	100%	0%
DMAP	81%	19%

Scheme 1. Base-specific distribution of 5-R-triazoles. Conditions: [alkyne] = 1.0 M; ratios: alkyne/azide/base/CuI—1.0/1.0/1.0/1.0.

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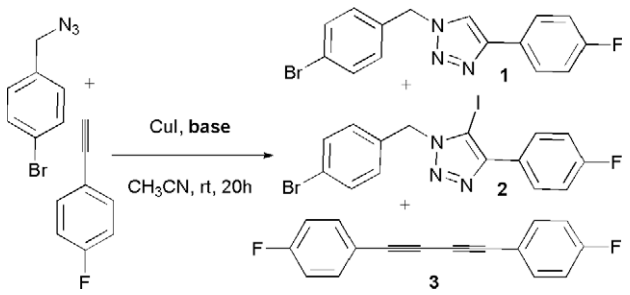
Table 1
Base/concentration effects on the 5-iodo-triazole formation[a]



Entry	Base	[Alkyne], mM	Product distribution[b] (%)		
			1	**2**	**3**
1	DMAP	1000	88	12	—
2	DMAP	35	64	30	6
3	DMAP	3.5	21	58	21
4	DMAP[c]	3.5	—	23	77
5	DMAP[d]	3.5	—	44	56
6	DMAP[e]	3.5	—	96	4
7	Pyridine	1000	84	16	—
8	Pyridine	3.5	76	24	—
9	DMA	1000	100	—	—
10	DMA	35	100	—	—
11	DMA	3.5	36	64	—
12	*i*Pr$_2$EtN	1000	100	—	—
13	*i*Pr$_2$EtN	35	100	—	—
14	*i*Pr$_2$EtN	3.5	100	—	—

[a] Ratios: alkyne/azide/base/CuI—1.0/1.0/1.0/1.0.
[b] Determined by ^{19}F NMR on a crude reaction mixture.
[c] Ratios: alkyne/azide/base/CuI—1.0/1.5/1.0/1.0.
[d] Ratios: alkyne/azide/base/CuI—1.0/3.0/1.0/1.0.
[e] Ratios: alkyne/azide/base/CuI—1.0/3.0/0.3/1.0.

plausible that the formation of 5-*I*-triazole takes place via a distinct Cu-intermediate, which is stabilized by DMAP.

Next, we varied the amount of CuI. Not surprisingly, decreasing CuI content led to inferior conversions. Increasing the amount of CuI to 2.0 equiv had no apparent impact on the rate of formation of the iodo-triazole **2**. Also, the application of CuCl proved to be inefficient in promoting the cycloaddition.

Furthermore, the distribution between **1** and **2** proved to be fairly insensitive to the nature of the solvent. Among the solvents screened (CH_3CN, THF, and DMSO), CH_3CN appeared the most efficient in terms of product distribution and conversion.

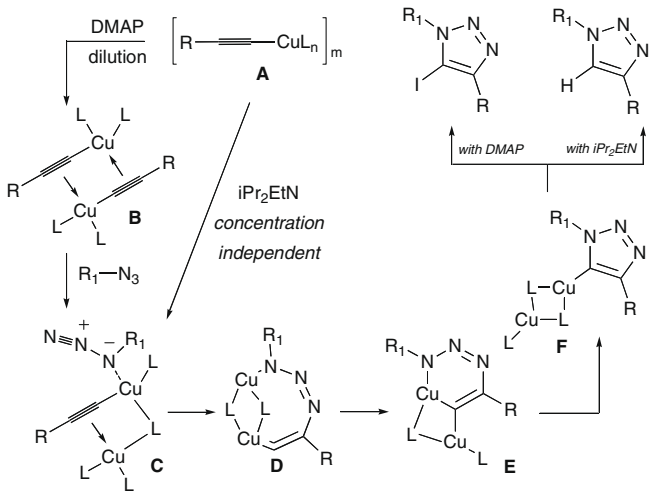
After some experimentation, we identified the concentration of the azide as one of the complementary factors in controlling the formation of 5-iodo-triazole. Conducting the reaction in the dilute solution (3.5 mM alkyne) with 1.5 equiv of the azide completely suppressed the formation of **1**, and afforded 5-*I*-triazole **2** as the only cycloaddition product (entry 4). Unfortunately, this set of conditions also promoted the homocoupling of the alkyne yielding diyne **3** (entry 4). This side reaction was previously reported for some Cu-catalyzed and Cu-promoted alkyne-azide cycloadditions,[3b,13] however, the effect of neither the base nor concentration had been examined. In order to suppress the formation of **3**, we conducted reactions under inert atmosphere (N_2) and/or using degassed CH_3CN, albeit with no success, as the amount of the produced diyne was largely unaffected.

However, further increasing concentration of the azide to 3.0 equiv (Table 1, entry 5) allowed to increase the amount of **2**, while decreasing the diyne **3** formation.[14] In order to suppress the formation of **3**, we varied the amount of DMAP. It appeared that higher concentrations of DMAP led to increased amounts of **3**, which is expected due to an enhanced rate of deprotonation of 4-fluorophenylacetylene. On the other hand, at 0.3 equiv of DMAP, the formation of **3** was significantly suppressed (Table 1, entry 6). Even though, the rate of the reaction was inhibited, 5-*I*-triazole **2** was obtained as the major product and the only cycloaddition product.

The effect of both pyridine and DMA resembled that of DMAP, yet neither was as efficient in promoting the formation of 5-*I*-triazole **2** (Table 1, entries 7–11). Although at 3.5 mM concentration DMA afforded 5-*I*-triazole as the major cycloaddition product, yet an appreciable amount of 5-*H*-triazole was still obtained. Importantly, the conversions with DMA and pyridine were inferior to those of DMAP. Neither DMA nor pyridine promoted the formation of diyne **3**, which is consistent with both of these bases being weaker than DMAP. Hünig's base (Table 1, entries 12–14) was completely insensitive to any concentration variations. Thus, DMAP appears to be the most efficient base in promoting the formation of 5-*I*-triazoles.

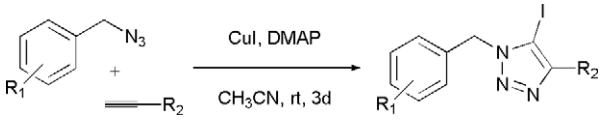
Although the exact mechanism of a typical CuI-catalyzed/promoted alkyne-azide cycloaddition remains to be clarified,[1a,2] the optimization studies (Table 1) provided some mechanistic insight about the formation of 5-*I*-triazoles (Scheme 2). It is largely accepted that copper-complexes could form various aggregates,[15] and therefore it is likely that at high concentrations these aggregates, **A**, might be responsible for promoting the alkyne–azide cycloaddition leading to the formation of 5-*H* triazoles. It is plausible that upon dilution, the Cu-acetylides **A** disaggregate to form a bis-copper acetylide complex **B** (Scheme 2). This complex **B** might be responsible for the formation of diyne **3** (Table 1), which becomes the major product in dilute media. This observation is supported by the mechanistic rationale for the terminal alkyne homocoupling (known as the Glaser alkyne homocoupling[16]), which is proposed to involve bis-copper acetylides. Furthermore, the use of DMAP, a strongly coordinating, sterically unbiased ligand (in comparison with Hunig's base) for Cu-complexes should assist in stabilization of **B**. In agreement with this proposal, we observed that the decrease in alkyne homocoupling was facilitated by the decrease in the amount of DMAP. Apparently, other bases are inferior to DMAP in aiding the stabilization of **B**, thus the formation of the diyne **3** was not observed.

Further, azides could also act as ligands and stabilize the subsequent copper complexes. Hence, it could be expected that the increase in the amount of azide would disrupt complex **B** and promote a formation of complex **C**. Relative inability of pyridine and DMA to stabilize **B**, as compared to DMAP, allows the azide to compete for the coordination site and afford **C**. This would explain the formation of **2** and the lack of **3** (Table 1, entries 8 and



Scheme 2. A tentative mechanism of 5-*I*-triazole formation.

Table 2
Synthesis of 5-*I*-triazoles[a]



Entry	R_1	R_2	Isolated yield (%)
1[b]	H	C_6H_5	77
2	Br	4-F-C_6H_4	24
3	4-MeO	C_6H_5	37
4	4-NO_2	C_6H_5	65
5[c]	4-NO_2	C_6H_5	78
6	H	*i*Pr	0
7	Br	*i*Pr	0

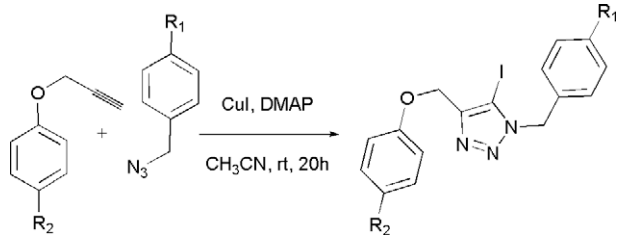
[a] Conditions: [alkyne] = 3.5 mM, ratios: alkyne/azide/DMAP/CuI—1.0/2.0/0.3/1.0.
[b] Reaction time 48 h.
[c] 3.0 equiv of azide.

11). It is plausible that **C** is still a bis-copper complex, since similar types of complexes were proposed in the formation of triazoles.[1a,2] The subsequent cascade probably proceeds from **D** to **E** to **F**, all of which are reminiscent to those suggested for the formation of the 5-*H* triazoles.[1a,2] Finally, DMAP, pyridine, and DMA, might provide extra stabilization of one or more of the **D**, **E**, and **F** complexes, (which was suggested for pyridine[2c]) and allow for an efficient intramolecular delivery of iodine to furnish 5-*I*-triazole, whereas the bulkier ligand *i*Pr_2EtN does not,[2c] thus leading to 5-*H*-triazole.

With optimized conditions at hand, we probed several alkyne–azide combinations (Table 2). The reaction rate was slow due to low concentrations that were required to achieve the exclusive formation of 5-*I*-triazole. Since product distribution was time independent, we increased the reaction times to 72 h, in order to achieve appreciable conversions. Chromatography-free removal of the reagents and unreacted starting materials afforded iodo-triazoles in low to moderate yields (entries 1–4). Increasing the amount of the azide from 2.0 equiv to 3.0 equiv had a marginal impact on the yield (entries 4 and 5). The aliphatic alkyne failed to react, as only the unchanged starting materials were recovered (entries 6 and 7).

In addition, we examined the effect of DMAP on the formation of 5-iodo-1,4-disubstituted triazoles using propargyl-containing substrates (Table 3). In general, these reactions are less efficient than the arylacetylene series (Table 2), however, the unreacted starting materials were easily recovered using flash column chromatography. Importantly, DMAP and low alkyne concentration were still the determining factors in facilitating the formation of

Table 3
Syntheses of 5-iodo-triazole from propargyl-containing substrates[a]



Entry	R_1	R_2	Isolated yield (%)
1	NO_2	H	22
2	MeO	H	12
3	*t*Bu	NO_2	34
4	H	MeO	39
5	NO_2	MeO	23
6	MeO	MeO	33

[a] [Alkyne] = 3.5 mM, ratios: alkyne/azide/DMAP/CuI—1.0/1.0/1.0/1.0.

iodo-triazoles. No alkyne homocoupling products were observed. The effect of varying other conditions, that is, concentrations of DMAP and CuI as well as the solvent was virtually identical to the results obtained with 4-fluoro-phenylacetylene.

In conclusion, we found that the identity of the organic base, as well as the concentration of the alkyne, could play major roles in determining the nature of the products in the CuI-promoted alkyne–azide cycloaddition. Low concentrations of the alkyne and the use of DMAP led to the formation of 5-*I*-triazoles as the only cycloaddition products. The expanded scope of this transformation will be reported in the due course.

Acknowledgments

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Supplementary data

Supplementary data (synthesis and characterization data for the described compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.089.

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