



A one-pot, copper-catalyzed azidation/click reaction of aryl and heteroaryl bromides in an environmentally friendly deep eutectic solvent



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ABSTRACT

In an effort to avoid the hazards of isolating and handling azides in click chemistry, many groups have turned to *in situ* generation of azides from halide precursors. This option is readily accomplished for alkyl azides, but is more challenging for aryl azides. In this paper, we discuss our success in transforming aryl bromides into 1,4-disubstituted triazoles employing DMEDA as a ligand with a copper catalyst in a deep eutectic solvent. Further, we are able to recycle the solvent, catalyst, and ligand several times, thereby increasing the attractiveness of this method.

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1. Introduction

The copper-catalyzed Huisgen reaction of an azide and an alkyne (CuAAC) has very rapidly become one of the preeminent reactions in organic chemistry.¹ It generally affords very good yields of the triazole product as a single regioisomer and tolerates a wide range of functionality, enabling its utilization in areas ranging from biological to materials research.² As broad as this application has been, the azide component remains a limitation. Organic azides are well known to be unstable and explosive compounds and thus their isolation is not desirable, particularly on larger scale.³ As a result, it is not surprising that many groups have explored ways to generate azides *in situ*.

For alkyl azides, this is usually simple as the azide anion is a good nucleophile. Thus, the combination of an alkyl halide with sodium azide in the presence of an alkyne and a copper catalyst accomplishes both the synthesis of the azide and the click reaction in one pot.⁴ The first reported example of this approach was in 2004 from the Fokin group.^{4c} They reported a microwave-assisted,

three-component, one-pot procedure in which the Cu(I) catalyst was prepared *in situ* by comproportionation of a Cu(0)/Cu(II) couple for the synthesis of 1,4-disubstituted 1,2,3-triazoles with 100% regioselectivity at 125 °C. The reaction times were quite short, and the products were easy to isolate in very high yield, although the reaction temperature was relatively high.

For aryl azides, the problem is more difficult, as direct nucleophilic displacement is not generally an option. In substrates which can undergo facile S_NAr reactions, Ramana has reported successful one-pot azidation/click tandems, but this scope is quite narrow.⁵ Substitution of other types of leaving groups have been reported, including iodoniums⁶ and diazonium salts,⁷ but in all of these cases hazardous reagents and/or poorly accessible starting materials still limit their general application.

The most ideal situation would be the direct conversion of an aryl halide to an aryl azide. Using the more reactive aryl iodides, the Fokin group in 2004 demonstrated *in situ* generation of aryl azides.⁸ Thus, treatment of an aryl iodide with sodium azide and a copper catalyst formed from copper sulfate, sodium ascorbate, and L-proline with sodium carbonate in DMSO/water at 60 °C formed the azide, which then underwent a CuAAC reaction with an alkyne. Again, yields were good, although reaction times were longer (overnight). Further, reaction was limited to aryl iodides, with aryl bromides failing to afford any triazole product.

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The following year, Liang and co-workers employed very similar reaction conditions which a change in ligand from proline to *trans*-*N,N'*-dimethyl-1,2-diaminocyclohexane to overcome this limitation and reported the first successful one-pot azidation/click reactions of aryl bromides.⁹ Since this report, these basic conditions (copper catalyst, ligand, and sodium ascorbate) have been used by several groups with little modification to perform these reactions, most frequently on simple benzenoid aromatics.¹⁰

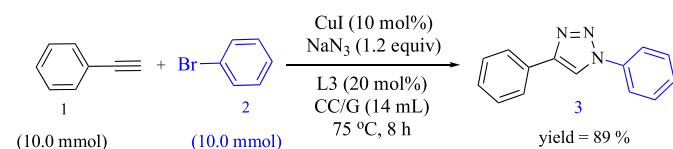
With one recent exception, to the best of our knowledge, there has been no attempt to develop a system in which the catalyst could be recycled or used at a lower loading than 10 mol% for the one-pot conversion of aryl bromides to aryl triazoles and in this one case, only one example was reported with an unusual alkyne, making its generality uncertain.¹¹ With this in mind and our ongoing interest in the combination of unusual solvents and catalyst recycling, we elected to study the application of a recyclable deep eutectic solvent (DES) based upon choline chloride and glycerol for the one-pot azidation/click reaction of aryl bromides.¹²

DES are a rapidly growing variation on the idea of ionic liquids.¹³ In general, they are comprised of a mixture of two or more components that exhibit a very dramatic depression in melting point compared to the pure components in the mixture, most typically via a combination of a salt with a hydrogen-bond donor or a salt with another metal salt capable of forming complex anions. Although many such solvents have been reported, choline chloride (CC – 2-hydroxyethyltrimethylammonium chloride) is the most widespread salt component as it is inexpensive, biodegradable, and available on large scale due to its use as a dietary additive in animal feed.^{13c,13f} While the CC/urea combination is the most frequently used,¹⁴ the combination with glycerol in a 1:2 M ratio is another very easily formed DES and was the focus of this work.¹⁵ It is worth noting that the CuAAC reaction has been reported before by Ilgen and Koenig using an unusual DES comprised of a 7: 2: 1 mixture of D- sorbitol, urea and NH₄Cl respectively, as a solvent and 5 mol% CuI as a catalyst yielding 91% of 1,4-disubstituted 1,2,3-triazole in 5 h.¹⁶ This reaction gave a 55% yield under the similar conditions with another deep eutectic solvent – L-carnitine/urea which was attributed to the higher reactivity of the melt (Scheme 1). In both cases, no attempt was made at catalyst and solvent recycling and the reaction was only studied for alkyl azides.

2. Results and discussions

In light of Koenig's success, we elected to pursue a one-pot azidation/click reaction in the easily available, inexpensive, and non-toxic DES choline chloride/glycerol (CC/G). We hoped to achieve conditions that would enable the conversion of aryl bromides to aryl azides and also be able to recycle the solvent and catalyst.

Initial screening was done using bromobenzene as the aryl halide and phenyl acetylene as the alkyne. Several different ligands commonly used in copper-catalyzed chemistry were explored, including proline, *N,N'*-dimethylethylenediamine (DMEDA), and phenanthroline. Of these, only DMEDA afforded the desired triazole product, fortunately in good yield (88%) (Table 1). While proline is a very common ligand for copper catalyzed chemistry, it has not been reported by any group to be effective for the one-pot azidation/click



Scheme 1. Scale-up Experiment.

Table 1
Survey of click reactions using deep eutectic Mixtures.

Entry	Modified conditions	Yield ^a (%)
1	ligand L1 instead of L3	0
2	ligand L2 instead of L3	0
3	standard conditions	88
4	without ligand	trace
5	5 mol% CuI	60
6	without CuI	0
7	CC/Urea instead of CC/Glycerol	11

^a Isolated yields.

reaction of aryl bromides – only aryl iodides. It seems likely that DMEDA, a stronger electronic rich sigma donor, is likely better able to both stabilize and activate the copper catalyst, compared to proline.¹⁷ As such, it is likely that other 1,2- *N,N'*-dimethylamines would also work under the present conditions.

Not surprisingly, both ligand and copper were important for reaction, but the catalyst loading could be lowered to 5 mol% with a modest decrease in yield (Table 1, entry 5), indicating that some further optimization of this parameter may be possible. It is also worth noting that use of the more common choline chloride/urea DES afforded a very low yield (Table 1, entry 7) of the triazole product, presumably due to the urea interfering in the catalytic cycle of the reaction.¹⁸

Armed with this success, a wider range of aryl bromide were explored including electron rich and deficient, ortho-substituted, heteroaromatic, and even dibromo arenes (Fig. 1). Yields ranged from excellent to modest. Not surprisingly, iodobenzene afforded a better yield when compared to the less reactive bromide (Fig. 1, compound 3). Interestingly, electron-deficient aryl bromides did not afford better yields when compared to the reaction with electron-rich *para*-bromoanisole (Fig. 1, compound 5) and ortho substitution did not appear to affect the reaction negatively based upon the examples studied. In the case of 3,6-dibromocarbazole, only a 40% yield of the monotriazole product (12), was observed, which can likely be attributed to its poor solubility in the DES.

The reaction between phenylacetylene and 2,4-dibromothiazole resulted in 4-bromo-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)thiazole (11) as a major product. For unequivocal determination of the regioselectivity of this reaction, compound 11 (the only isomer formed) was crystallized from an ether solution layered with pentane at 4 °C and the resulting crystal subjected to x-ray crystallography (Fig. 2).

To further probe the utility of these reaction conditions, the reaction of various alkynes with different aryl bromides were performed (Fig. 3). Various functionalized alkynes afforded reasonable yields of the anticipated triazoles. 1-Ethynylcyclohexene and 1-hexyne were found to react successfully with heteroaryl 3-bromothiophene (17 and 24) resulting in yields of the predicted products comparable to those observed with the generally more

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