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Fast dye salts provide fast access to azidoarene synthons in multi-step one-pot tandem click transformations

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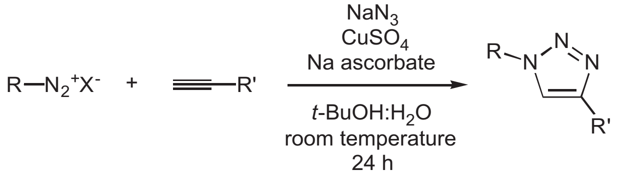
ABSTRACT

This study examined whether commercially available diazonium salts could be used as efficient aromatic azide precursors in one-pot multi-step click transformations. Seven different diazonium salts, including Fast Red RC, Fast Blue B, Fast Corinth V and Variamine Blue B were surveyed under aqueous click reaction conditions of $CuSO_4$/Na ascorbate catalyst with 1:1 *t*-BuOH/H_2O solvent. Two-step tandem reactions with terminal alkyne and diyne co-reactants led to 1,2,3-triazole products in 66–88% yields, while three-step tandem reactions with trimethylsilyl-protected alkyne and diyne co-reactants led to 1,2,3-triazole products in 61–78% yields.

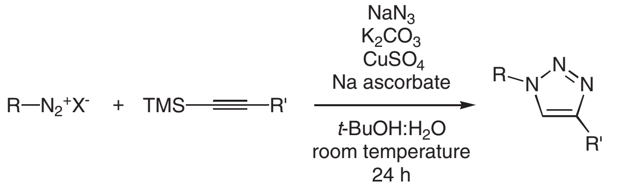
The high chemospecificity of the copper-catalyzed Huisgen 1,3-dipolar cycloaddition, commonly termed the Sharpless–Meldal 'click' reaction,[1–4] has proven amenable to the development of tandem click reactions involving multiple reaction steps within a single reaction pot. Due to the potential danger in isolating small organic azides,[1,5] such reactions often involve the in situ formation of azide intermediates that are subsequently converted into 1,2,3-triazole products. Established organic azide precursors for multi-step one-pot click transformations include alkyl, benzylic,[6–8] allylic[8] and α-carbonyl halides,[9] as well as amines,[10–12] boronic acids,[13] epoxides[14,15] and alcohols.[16]

While a variety of precursors able to generate aliphatic azides have been reported recently in the literature, examples of synthons able to efficiently generate aromatic azides in the context of tandem click reactions are limited in comparison.[17–19] Hence, the goal of this investigation was to identify a new class of synthons able to serve as aromatic azide precursors for such processes. Because a variety of aromatic diazonium salts are commercially available and represent an interesting diversity of chemical functionality, this study aimed to determine whether such compounds could be used directly as efficient aromatic azide precursors in one-pot tandem click reactions. In this study both two-step and three-step one-pot click transformations were evaluated: a two-step process (Scheme 1) involving the in situ formation of organic azide followed by copper-catalyzed Huisgen 1,3-dipolar cycloaddition, and a three-step process (Scheme 2) that additionally incorporates a base-catalyzed trimethylsilylalkyne deprotection step.[20–23]

Diazonium salts are known to undergo reactions such as diazo coupling with electron-rich partners, a commonly used approach to prepare pH indicators as well as colorfast fabric dyes (hence the 'fast dye salt' moniker).[24] They can also undergo a variety of nucleophilic substitution reactions, including hydrolysis.[25,26] Although substitution by the azide nucleophile used in these reactions was predicted to be rapid, the potential for competitive deleterious side reactions was a concern. Hence, an important component of this investigation was to determine whether



Scheme 1. Two-step tandem click transformation.



Scheme 2. Three-step tandem click transformation.

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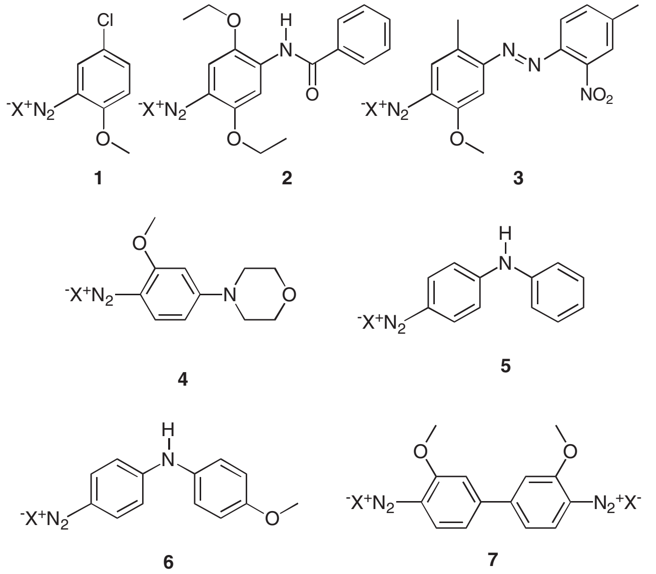


Figure 1. Diazonium salts surveyed in this investigation. For **1**, **2**, **3**, **4**, and **7** $X^- = 0.5\ ZnCl_4^{2-}$; for **5** $X^- = HSO_4^-$; for **6** $X^- = Cl^-$.

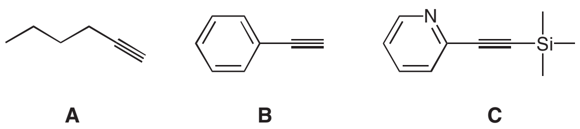


Figure 2. Alkynes surveyed in this investigation.

diazonium salts utilized as aromatic azide precursors in multi-step one-pot click reactions would successfully undergo substitution with azide followed by Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition while avoiding both hydrolysis and diazo coupling side reactions under the room-temperature aqueous conditions employed.

As illustrated in Figure 1, the diazonium salt synthons surveyed in this study include Fast Red RC (**1**), Fast Blue BB (**2**), Fast Corinth V (**3**), 2-methoxy-4-morpholinobenzene diazonium chloride (**4**), Variamine Blue RT (**5**), Variamine Blue B (**6**) and the bifunctional analog Fast Blue B (**7**). The alkyne reactants examined in this study are shown in Figure 2. The aliphatic terminal alkyne 1-hexyne (**A**) and the aromatic terminal alkyne phenylacetylene (**B**) were used to survey two-step one-pot tandem reaction conditions.[27] Three-step one-pot tandem reaction conditions were examined using 2-trimethylsilylethynylpyridine (**C**), a synthon previously reported to efficiently participate in tandem click reactions involving trimethylsilyl deprotection.[22,23]

Table 1 summarizes the utility of the diazonium salts **1**-**7** as the azide sources in two-step and three-step one-pot tandem click reactions with terminal and trimethylsilyl-protected alkyne reactants **A**, **B** and **C**. These reaction setups involved the simple addition of diazonium and alkyne reactants to 1:1 solutions of *tert*-butanol/water containing 20 mol % $CuSO_4$ and 40 mol % sodium ascorbate. Only upon addition of the final reagent, sodium azide, did vigorous evolution of gas occur, signifying the rapid completion (within minutes) of the first step of the tandem reaction. Each reaction was stirred for 24 h, and the products isolated via simple extraction procedures.[28]

Because the reactions were run at room temperature, there was some concern that electron rich arene reactants might lead to diazonium coupling side reactions competing with the desired Cu-catalyzed cycloaddition. These concerns were found to be unwarranted, in that no major differences in yield or product purity were observed between the aliphatic alkyne **1** and the aromatic alkyne **2**. For reactions with trimethylsilyl-protected **3**, simple addition of potassium carbonate to the reaction mixtures promoted the third tandem step of alkyne deprotection. In comparing the results of the two-step and three-step transformations it was concluded that the addition of a third step in the tandem process did not negatively impact overall product yield or purity. As summarized in Table 1, an appreciable diversity of arene units can be directly incorporated into 1,2,3-triazole products using commercially available diazonium salts **1**-**6**. Reactions of the diazido salt **7** gave bis-functionalized products in yields largely analogous to the monofunctionalized derivatives, even though the formation of such products required twice the overall number of chemical transformations. Identity of the diazonium salt counterion did not impact reaction efficiency.

No differences in product purity were observed by ^1H NMR between one-pot procedures where all reagents were introduced at once versus an analogous time-delayed procedure where diazonium salts and sodium azide were allowed to react for 10 min in water before the remaining reactants were introduced. This highlights the orthogonality of each step of these tandem two- and three-step reactions. In addition, withholding either catalyst or alkyne co-reactant from each reaction resulted in the isolation of only aromatic azide intermediate products as observed by ^1H NMR. It is noteworthy that the yields of isolated azide intermediates prepared in control studies ranged from 81% to 91% (Table 2), largely reflecting the commercial purity of these reactants. No attempts were made to purify the commercially available diazonium salts before use. Hence, the efficiency of azide formation from such precursors does significantly impact triazole product yields in the tandem reactions.

Because aromatic azides are commonly prepared from aromatic amines via diazotization reactions in acidic media, attempts were made to utilize such crude diazonium salt solutions or suspensions directly in tandem click reactions. Such attempts were unsuccessful, likely due to the acidic environment required of the diazotization reaction. No attempts were made to isolate any of the diazotization reaction intermediates from their acidic media. In spite of the observed purity issues for several of the commercially available dyes utilized, the ability to introduce diazonium reactants directly as solids in tandem click reactions proved to be a practical and efficient method for preparing a variety of aromatic azides in situ.

In summary, commercially-available diazonium salts have been identified as useful organic azide precursors in tandem click transformations. A series of mono- and difunctionalized fast dye salts produced 1,2,3-triazole products in good yields under both two-step one-pot tandem reactions with terminal alkyne reactants and three-step one-pot tandem reactions with trimethylsilyl-protected alkyne reactants. These findings establish diazonium salts as new and practical additions to a recently evolving class of synthons able to generate organic azide intermediates in situ for participation in common click reactions that avoid the need for isolating potentially shock-sensitive intermediate azido and diazido intermediate reactants. Utilizing such synthons in tandem click reactions serve as an efficient means by which to prepare 1,4-disubstituted-1,2,3-triazole compounds with medicinally relevant subunits, due to the diversity of structural functionality represented in commercially available diazonium salts.

Table 1
Summary of tandem reactions surveyed

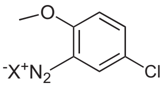
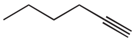
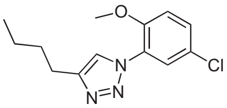
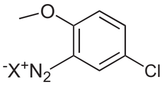
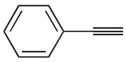
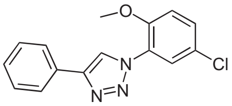
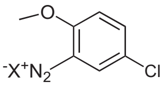
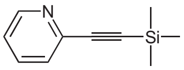
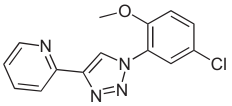
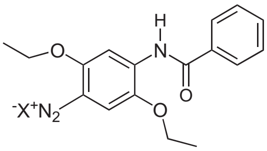
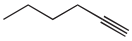
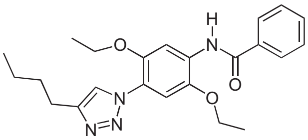
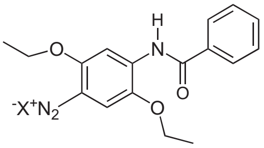
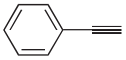
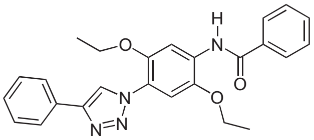
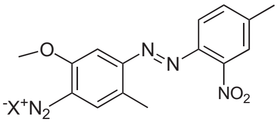
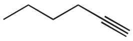
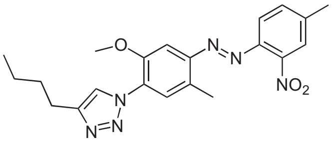
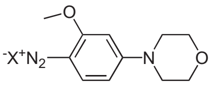
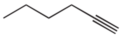
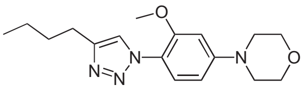
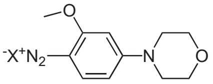
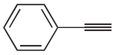
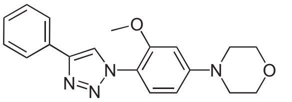
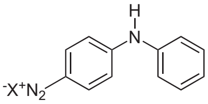
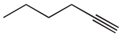
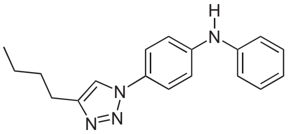
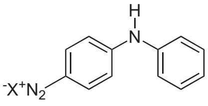
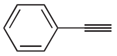
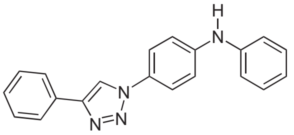
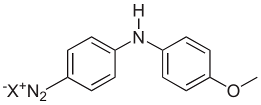
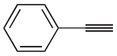
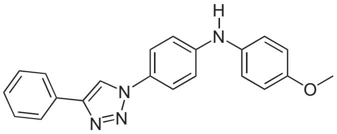
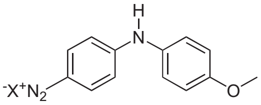
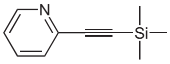
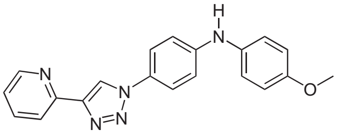
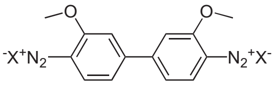
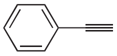
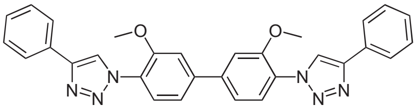
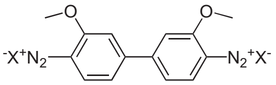
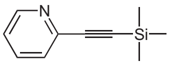
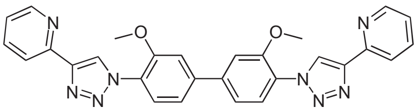
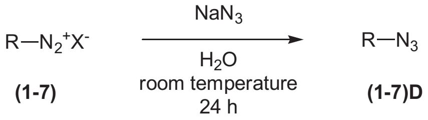
Entry	Diazonium salt	Alkyne	Condition	ID	Structure	Yield (%)
1			*a*	**1A**		88
2			*a*	**1B**		71
3			*b*	**1C**		78
4			*a*	**2A**		83
5			*a*	**2B**		68
6			*a*	**3A**		86
7			*a*	**4A**		74
8			*a*	**4B**		66
9			*a*	**5A**		82
10			*a*	**5B**		70
11			*a*	**6B**		67
12			*b*	**6C**		63
13			*c*	**7B**		66

Table 1 (*continued*)

Entry	Diazonium salt	Alkyne	Condition	ID	Structure	Yield (%)
14			*d*	**7C**		61

Reaction conditions: (*a*) 1.0 mmol diazonium salt, 1.2 mmol sodium azide, 1.2 mmol alkyne, 0.2 mmol $CuSO_4$, 0.4 mmol sodium ascorbate, 5 mL *t*-BuOH, 5 mL H_2O, 24 h, room temperature; (*b*) identical to *a* with addition of 1.2 mmol K_2CO_3; (*c*) identical to *a* except with 0.5 mmol diazonium salt; (*d*) identical to *b* except with 0.5 mmol dizonium salt.

Table 2
Isolated yields of azide reactants prepared from diazonium salts



Azide derivative	Isolated yield (%)
1D	89
2D	90
3D	89
4D	90
5D	91
6D	81
7D	88

Acknowledgments

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Supplementary data

Experimental procedures and characterization including copies of ^1H NMR and MS spectra for all reported azide and triazole products are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.069.

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28. *General procedure*: To a 20 mL scintillation vial was added (in order) $CuSO_4$, sodium ascorbate, diazonium salt, water, *tert*-butanol, and alkyne reactant (amounts as noted in Table 1). Lastly, sodium azide was added with stirring, resulting in a rapid evolution of gas from the vial over approximately 10 min. After the majority of gas evolution had subsided, the vial was loosely sealed with a screw cap and continued to stir rapidly at room temperature. After 24 h the reaction was extracted between methylene chloride and 5% aqueous ammonium hydroxide solution, and the aqueous layer was washed a second time with methylene chloride. The combined organic layers were dried over magnesium sulfate and the solution isolated via gravity filtration through fluted filter paper into a round bottom flask. Volatiles were removed via rotary evaporation to give the final 1,2,3-triazole product.