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Unprecedented Cu-Catalyzed Coupling of Internal 1,3-Diynes with Azides: One-Pot Tandem Cyclizations Involving 1,3-Dipolar Cycloaddition and Carbocyclization Furnishing Naphthotriazoles†

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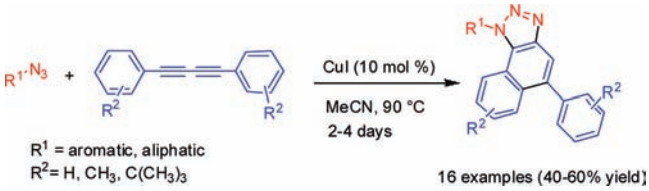
ABSTRACT



A one-pot protocol for the synthesis of triazole-annulated polyheterocycles via metal-catalyzed coupling of internal 1,4-disubstituted 1,3-diynes and organic azides has been described. The mechanistic rationale for the reaction suggests tandem cyclizations involving copper-catalyzed cycloaddition and 6-*endo* carbocyclization reactions. The cascade cyclization leads to an increase in molecular complexity to furnish naphtho[1,2-*d*]triazoles in satisfactory yields. The generality of the method has been demonstrated by using a series of aromatic/aliphatic azides and symmetrical internal 1,3-diynes.

In the past decade, azide alkyne Huisgen 1,3-dipolar cycloaddition reaction and its variant click chemistry have evolved as powerful strategies with many applications in modern chemistry, drug discovery, macromolecules, radiopharmaceuticals, material sciences, and biology.[1] While the former startegy involves coupling under thermal conditions, the click chemistry conventionally involves copper(I)-catalyzed coupling of azide with terminal alkynes leading to the regioselective formation of 1,4-disubstituted 1,2,3-triazoles;[2] however, in subsequent studies, the ruthenium-catalyzed reaction was found to furnish the opposite regioselectivity furnishing 1,5-disubstituted 1,2,3-triazoles.[3] Interestingly, the Ru catalyst also facilitated fusion of azides with internal alkynes furnishing 1,4,5-trisubstituted 1,2,3-triazoles, a limitation generally observed with conventionally used Cu catalysts. Indeed, Nolan et al.[4] used a NHC−Cu complex as a catalyst for the cycloaddition reacton involving internal alkynes. Later, several groups[5] extended application of click chemistry to diynes and reported coupling of terminal 1,3-diynes[6] with azides under Cu-catalyzed conditions to furnish regioselective 4-ethynyl-1,2,3-triazoles. Recently, in a similar study using terminal diynes, syntheses of bis-triazoles were carried out by employing two consecutive Cu-catalyzed cycloaddition reactions in one pot involving

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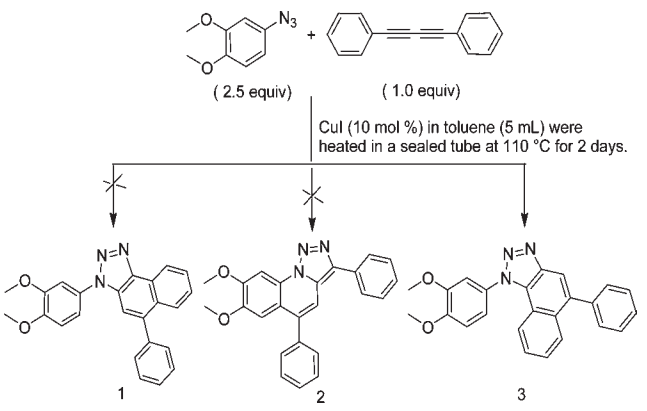
monotriisopropylsilyl-protected diynes and azides.[7] It is worth mentioning that after the first cycloaddtion with terminal 1,3-diyne the silyl group from the resulting 4-ethynyl-protected 1,2,3-triazole was removed in situ followed by second engagement of the terminal alkyne at *C*-4 with azides to afford bistriazole. Indeed, despite the successful applications of Cu-catalyzed 1,3-dipolar cycloaddition reactions to terminal diynes, their application to internal 1,3-diynes has not yet been investigated.

We envisaged that use of internal 1,4-disubstituted-1,3-diynes may trigger sequential cyclizations by first forming a triazole with the azide via cycloaddition followed by carbocyclizaton involving alkynyl residue originating either from *C*-4 or *C*-5 of the triazole and the nearest phenyl ring present either at *N*-1 or at *C*-5/*C*-4. Indeed, depending on the regioselective formation of the resulting triazole, the second cyclization may furnish either naphthotriazole[8] or pyridotriazole[9] as an annulated polyheterocycle. In recent years, an increasing number of studies have been carried out to develop a cascade reaction in one pot for the synthesis of triazole-annulated polyheterocycles,[10] which in turn can be used to obtain bioactive leads. Thus, the search for a concise and more efficient method for the synthesis of 1,2,3-triazole-annulated polyheterocycles in one-pot reactions remains a challenging task for chemists. In this paper, we describe Cu-catalyzed coupling of internal 1,3-diynes with organic azides furnishing naphthotriazoles via sequential cyclizations involving cycloaddition and carbocyclization in one pot. The studies are a continuation of our interest in the synthesis of triazole/indole/pyrrole-based annulated polyheterocycles in minimal steps involving either multistep or via sequential cyclizations/multicomponent reactions in one pot.[11]

In our initial studies, we treated 4-azido-1,2-dimethoxybenzene with 1-(4-phenylbuta-1,3-diynyl)benzene in the presence of CuI in toluene at 110 °C. The progress of reaction was monitored by TLC, and after 3 days of stirring, we observed the appearance of a new spot along with unreacted 1,3-diyne as the other component. After workup and purification by column chromatography, we observed a new product with a molecular weight of 381.15 Da in 45% isolated yield along with the recovery of unreacted 1,3-diyne in 20% isolated yield (Scheme 1). Since the ^{13}C NMR spectrum showed the absence of any alkyne carbon, we envisaged that triazole formation may have been followed by carbocyclization. However, depending on the regioselectivity of the triazole formation during Cu-catalyzed 1,3-dipolar cycloaddition, there can be a distinct possibility for three probable structures **1**−**3** (Scheme 1) with identical molecular weights following carbocyclization. The structure of the product so obtained was elucidated by the combined use of various homo- and

Scheme 1. Copper-Catalyzed Coupling of 1-(4-Phenylbuta-1,3-diynyl)benzene with 4-Azido-1,2-dimethoxybenzene



heteronuclear two-dimensional NMR experiments. Out of the three probable structures, structure **3**, 1-(3,4-dimethoxyphenyl)-5-phenyl-1*H*-naphtho[1,2-*d*][1,2,3]triazole, was thus designated to be the product arising from sequential cycloaddition and carbocyclization in one pot.

Figure 1 highlights a few selected HMBC and NOE correlations required for the confirmation of structure **3**.[12] This was further supported by performing restrained molecular dynamics calculations using Discover 3.0 software. Distance restraints were derived on the basis of NOE intensities.[12]

The mechanistic details for this unprecedented copper-catalyzed synthesis of triazole involving internal 1,3-diyne need much more study since involvement of copper acetylides is not possible. Based on our observation, we propose a plausible mechanism for the formation of **3** as depicted in Figure 2. The first step of the reaction involves regioselective formation of triazole via cycloaddition reaction resulting in an intermediate 1-(3,4-dimethoxyphenyl)-5-phenyl-4-(2-phenylethynyl)-1*H*-1,2,3-triazole **4**. Copper complex then presumably forms via alkyne moiety

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(12) See the Supporting Information.

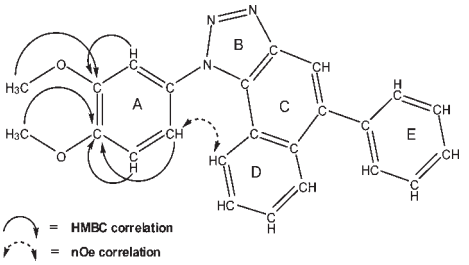


Figure 1. Few important **HMBC** and **NOE** correlations for **3**.

in the presence of CuI, thereby enhancing its electrophilicity. The resulting electron-deficient triple bond then undergoes nucleophilic attack by the carbon from the phenyl ring originating from the *C*-5 of the triazole, thereby facilitating intramolecular 6-*endo*-cyclization to furnish **3**. Interestingly, **3** appeared to be a useful template for the generation of novel triazole-annulated polyheterocycles in one pot via tandem cyclization reactions. This led us to optimize the reaction conditions for improving the yield of napthotriazole **3** (Table 1). We carried out this reaction by employing a variety of copper salts, additives, and solvents. While examining the effect of solvent, we observed an increase in the yield of **3** to 58% in acetonitrile (entry 5). Similarly, among various copper catalysts investigated, CuI produced the best results. This gets further support from the fact Cu(I) species when generated in situ by a redox reaction involving $FeCl_3$ and copper metal in water[11c] furnished **3** in 40% isolated yield (entry 3). Attempts to further improve the yield by either increasing the concentration of azides or by extending reaction timings were not fruitful. Thus, the optimal conditions involved treatment of azide with 1,3-diyne in the presence of CuI in acetonitrile under reflux for 2 days. Indeed, the long reaction time, moderate yields, and absence of intermediate **4** in the reaction mixture prompted us to explore the role of copper in both steps. Accordingly, we initially examined the formation of **3** under thermal conditions in acetonitrile in the absence of catalyst. The uncatalyzed reaction furnished traces (< 10%) of product **3** as evident by HPLC even after 3 days of reflux (entry 6). Next, in order to examine the effect of elevated temperatures on the formation of **3** in the absence of catalyst, we carried out the reaction in toluene under reflux for 2 days. The uncatalyzed reaction was very sluggish and furnished a mixture of products with the formation **3** in 25% isolated yield (entry 2). This is in contrast to 45% isolated yield obtained in the presence of copper catalyst in toluene under reflux (entry 1). Our findings strongly suggest that in the absence of copper catalyst and under thermal conditions formation of **3** is extremely sluggish; however, addition of Cu catalyst increased the yield of **3** in toluene from 25% to 45% and in acetonitrile from < 10% to 58%.

Once the reaction conditions for the synthesis of **3** were optimized, we then proceeded with the utility of the method to generate naphthotriazole-based heterosystems. For this we synthesized 16 compounds (**3a**−**p**) based on **3**

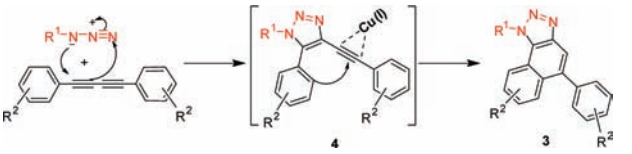


Figure 2. Plausible mechanism for the copper-catalyzed tandem cyclizations.

Table 1. One-Pot Tandem Cyclizations Involving 4-Azido-1, 2-dimethoxybenzene (2.5 Equiv) and 1-(4-Phenylbuta-1, 3-diynyl)benzene (1.0 Equiv) To Form Naphtho[1,2]triazole **3**: Optimization of Reaction Conditions

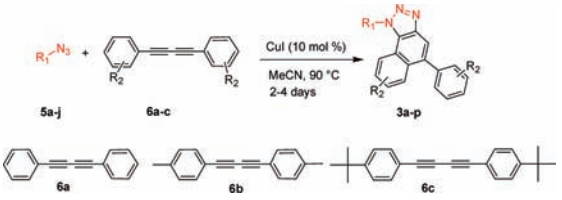
entry	reaction conditions	temp (°C)	time (d)	product (%)
1	CuI in toluene	reflux	2	45
2	toluene	reflux	2	25
3	$Cu/FeCl_3$ in H_2O	reflux	2	40
4	CuI in MeCN	rt	2	NR[a]
5	CuI in MeCN	reflux	2	58
6	MeCN	reflux	3	<10[b]
7	CuI in THF	reflux	2	NR[a]
8	$CuSO_4$/sodium ascorbate in H_2O/^{t}BuOH	rt	2	NR[a]
9	$CuSO_4$/sodium ascorbate in H_2O/^{t}BuOH	reflux	2	NR[a]
10	$CuSO_4$/sodium ascorbate in H_2O/MeCN	reflux	2	NR[a]
11	$CuI/Cu(OAc)_2$ in MeCN	reflux	2	NR[a]
12	$PdCl_2$ in MeCN	reflux	2	NR[a]

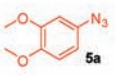
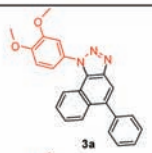
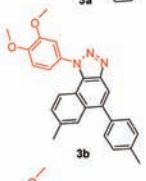
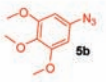
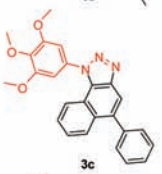
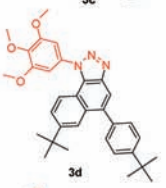
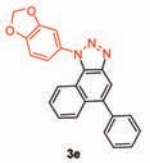
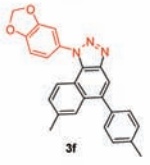
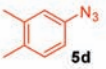
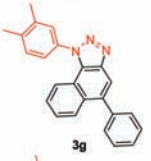
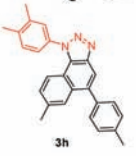
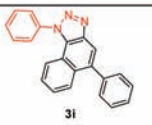
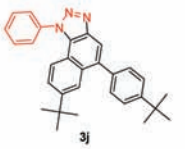
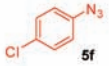
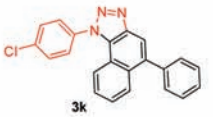
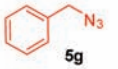
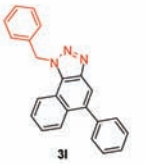
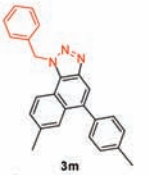
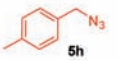
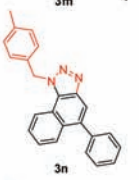
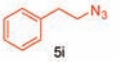
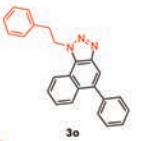
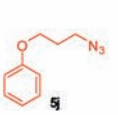
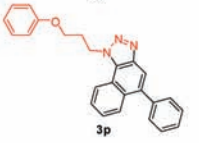
[a] NR = no reaction. [b] Based on HPLC.

by treating a series of aliphatic and aromatic azides with symmetrical 1,3-diynes. The compounds were purified by silica gel chromatography and characterized by NMR spectroscopy. As shown in Table 2, most of the reactants examined provided naphthotriazoles in moderate yield. For all of the reactions, we were able to recover unreacted diynes which were found to be suitable for reuse. In general, no significant difference of reactivity was observed for the examined aromatic azides, aliphatic azides, and 1,3-diynes with varied electronic properties. Aromatic azides furnished **3** in yields ranging from 40 to 60%, whereas aliphatic azides furnished products in 47−55% yield. Similarly, whereas 1-(4-phenylbuta-1,3-diynyl)benzene furnished products in 42−58% yield, introducing an electron-donating substituent on the phenyl rings furnished products in 40−60% yield. Replacing organic azides with sodium azide failed to facilitate tandem cyclizations under Cu-catalyzed conditions.

In summary, an experimentally convenient copper-catalyzed process for the regioselective synthesis of naphthotriazole from organic azides and internal 1,3-diynes has been developed. The salient features of the strategy comprise Cu-catalyzed one-pot sequential cyclizations via 1,3-dipolar cycloaddition and 6-*endo* carbocyclization. The generality of the method has been demonstrated by using a series of aromatic/aliphatic azides and symmetrical internal 1,3-diynes.

Table 2. One-Pot Tandem Cyclizations Involving Copper-Catalyzed Cycloaddition and Carbocyclization To Furnish Diverse Naphthotriazoles



entry	5	6	time	product	yield (%)[a]
1	 5a	6a	2 d	 3a	58
2	5a	6b	3 d	 3b	45
3	 5b	6a	3 d	 3c	48
4	5b	6c	2 d	 3d	60
5	 5c	6a	3 d	 3e	56
6	5c	6b	3 d	 3f	48
7	 5d	6a	3 d	 3g	51
8	5d	6b	4 d	 3h	50
9	 5e	6a	3 d	 3i	42
10	5e	6c	4 d	 3j	40
11	 5f	6a	3 d	 3k	46
12	 5g	6a	3 d	 3l	54
13	5g	6b	3 d	 3m	47
14	 5h	6a	3 d	 3n	55
15	 5i	6a	4 d	 3o	50
16	 5j	6a	3 d	 3p	52

[a] Isolated yield based on bis-alkyne, NMR yield using mesitylene as an internal standard.

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Supporting Information Available. Experimental procedure, characterization data (NMR, IR, HRMS), copies of ^{1}H and ^{13}C NMR spectra, and restrained MD calculation details. This material is available free of charge via the Internet at http://pubs.acs.org