

One-Pot Synthesis of 1,2,3-Triazoles from Benzyl and Alkyl Halides, Sodium Azide and Alkynes in Water Under Transition-Metal-Catalyst Free Reaction Conditions

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Abstract: In the absence of any catalysts and additives, one-pot synthesis of 1,2,3-triazoles from benzyl and alkyl halides, sodium azide and alkynes in water was developed. The reactions of terminal arylalkynes, sodium azide with benzyl chlorides and bromides generated the corresponding regioselective 1,4-disubstituted triazoles in excellent yields, but terminal aliphatic alkynes afforded the mixture of regioisomers (1,4-disubstituted and 1,5-disubstituted triazoles). For the reactions of primary aliphatic bromides, sodium azide and phenylacetylene, the ratio of 1,4- to 1,5-isomers ranging from 57 : 43 to 100 : 0 indicated 1,4-disubstituted regioselectivity of the reaction was raised with the increase of the carbon chain in primary aliphatic bromides. The present procedure does not require isolation of the azide intermediates and may prove to be especially useful when unstable low-molecular weight and polyvalent azides are needed. Furthermore, it is an ideal environmental benign reaction system only using water as solvent without any catalysts and additives.

Keywords: 1,2,3-triazoles, one-pot synthesis, benzyl and alkyl halides, sodium azide, alkynes, transition-metal-free, water.

INTRODUCTION

1,2,3-Triazoles have been widely used in synthetic intermediates and industrial applications, such as dyes, anticorrosive agents, photostabilizers, photographic materials, and agrochemicals [1]. Although the 1,2,3-triazole structural moiety does not occur in nature, it may display biological activities and there are numerous examples in the literature including anti-HIV activity [2], anti-microbial activity against Gram positive bacteria [3], anti-allergic [4], anti-convulsant [5], β -lactamase inhibitory [6], selective 3 adrenergic receptor agonism [7], and so on [8].

Numerous synthetic methods for the preparation of 1,2,3-triazole derivatives have been developed. Among them Huisgen 1,3-dipolar cycloaddition between an alkyne and an azide is the classical and extensively used method [9]. However, the regioselectivity of this cycloaddition reaction is generally low and the reaction usually leads to a mixture of 1,4- and 1,5-regioisomers [10]. In 2002, K. B. Sharpless and M. Meldal improved the regioselectivity of the reactions by Cu(I)-catalyzed ligation (click chemistry) of organic azides and terminal alkynes [11]. Exclusive regioselectivity, wide substrate scope, mild reaction conditions, effective catalysis system (accelerates the reaction upto 10^7 times), and high yields have made it the method of choice for making permanent connections by means of 1,4-disubstituted 1,2,3-triazoles in the presence of copper catalyst. The catalyst can be directly introduced as a Cu(I)

salt (CuI or CuBr) [12] or generated *in situ* by reduction of Cu(II) salts [13], comproportionation of Cu(0) and Cu(II) [14], Cu(0) nanosize cluster [15], Cu(II) salt [16], or Ru(II) complex [17]. It should be noted that the high cost of transition metal catalysts coupled with the toxic effects associated with many transition metals has led to an increasing interest in transition-metal-catalyst-free organic synthetic reactions recently [18].

Although organic azides are generally safe compounds, those of low molecular weight can be unstable and, therefore, difficult to handle [19]. This is especially true for small molecules with several azide functionalities that would be of much interest for the generation of polyvalent structures. Thus, a method that avoids isolation of organic azides is desirable. *In situ* generation of organic azides from suitable precursors followed by addition of alkyne in one-pot, to form the corresponding 1,2,3-triazoles would avoid the difficulties associated with the explosive nature of the azides. Maksikova described an *in situ* formation of 1,2,3-triazoles from alkyl halides, alkynes and sodium azide [20]. This method requires the reagents to be heated at high temperatures for extended periods of time, resulting in a mixture of regioisomers and giving low yields. Recently, V. V. Fokin demonstrated a very effective one-pot preparation of 1,4-disubstituted 1,2,3-triazoles from a variety of readily available aromatic and aliphatic halides catalyzed by a combination of Cu(I) and L-proline without isolation of potentially unstable organic azide intermediates [13a]. Meanwhile, E. Van der Eycken *et al.* also found that a microwave irradiation could accelerate the one-pot reaction and a series of 1,4-disubstituted-1,2,3-triazoles were generated from corresponding alkyl halides, sodium azide, and alkynes in the presence of Cu(I) [13b]. Most recently,

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Kacprzak developed an efficient one-pot method for the synthesis of 1,4-disubstituted-1,2,3-triazoles from benzyl or alkyl halides, sodium azide, and alkynes in the presence of Cu(I) in DMF [21]. To the best of our knowledge, there is no report on the one-pot ligation reaction of activated organic halides, sodium azide, and alkynes under catalyst-free reaction conditions.

Organic reactions carried out in aqueous media have received considerable attention since last decade [22]. Except for economical and environmental concerns, extensive studies have revealed that a number of organic reactions proceed more rapidly and efficiently in aqueous solution than in organic solvents [23]. This is demonstrated especially in Grieco's studies of Diels-Alder reactions in water [24]. Here we wish to report an efficient, safe and green one-pot synthesis of 1,2,3-triazoles from benzyl and alkyl halides, sodium azide and alkynes in water under transition-metal-catalyst free reaction conditions without any additives. The reactions underwent smoothly to generate the corresponding 1,2,3-triazole derivatives in high yields (Scheme 1).

RESULTS AND DISCUSSION

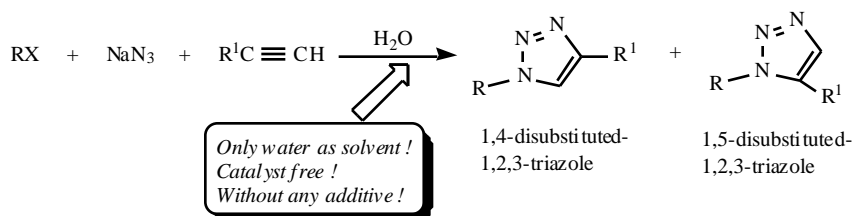
In our initial exploration, the reaction between benzyl chloride, sodium azide and phenylacetylene was chosen as a model reaction. The alkyne, alkyl halide and sodium azide with 1:1:1.1 molar ratios were suspended in distilled water with vigorously stirring at 100 °C for 24 h, and the corresponding 1,2,3-triazoles were obtained in good yields. The products were crystallized from the reaction mixture and were isolated by simple filtration. The results were listed in Table 1.

When a terminal arylalkyne, such as phenylacetylene, *p*-methylphenylacetylene, *p*-bromophenylacetylene, or *p*-chlorophenylacetylene was employed to react with benzyl halides including benzyl bromide, benzyl chloride, *p*-methylbenzyl chloride, or *p*-nitrobenzyl chloride, the corresponding 1,4-disubstituted 1,2,3-triazoles were isolated as regioselective products in excellent yields under the present reaction conditions (Table 1, entries 1–7). However, same reactions performed in DMF and C₂H₅OH led to slower reactions and usually yielded a mixture of regioisomers in 88% and 15% yields, respectively (Table 1, entry 1). Similar results were also observed for the reaction of phenylacetylene with azidobenzene in toluene under reflux, which gave two regioisomers in approximately 1:1 ratio [25]. The experimental data in Table 1 also indicated that the substituents attached to the aryl ring of the benzyl halide derivatives apparently affect the cycloaddition reactions with the electron-withdrawing groups promoting the reactions and

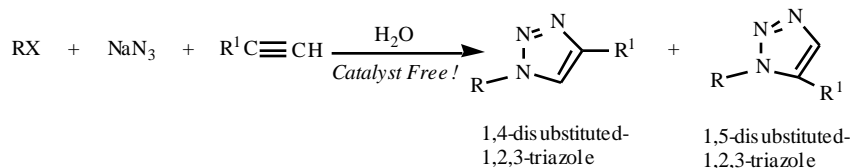
electron-donating groups impeding the reactions. (Table 1, entries 6 and 7). When the reactions were switched from terminal arylalkyne to terminal aliphatic alkyne, such as 1-decyne and 1-octyne, the mixture of 1,4-disubstituted and 1,5-disubstituted 1,2,3-triazoles were formed with ratio around 1:1 in good yields (Table 1, entries 9 and 10). The reactivity of primary aliphatic halides was found to be *n*-C₄H₉I > *n*-C₄H₉Br > *n*-C₄H₉Cl, which is consistent with the expected reactivity. *n*-Butyl chloride was essentially unreactive, probably due to the stronger carbon-chlorine bond (Table 1, entries 11–13).

Besides benzyl halides derivatives, primary aliphatic bromides, such as *n*-C₄H₉Br, *n*-C₆H₁₃Br, *n*-C₈H₁₇Br, *n*-C₁₀H₂₁Br, *n*-C₁₂H₂₅Br, *n*-C₁₆H₃₃Br, also reacted with phenylacetylene and sodium azide under the standard reaction conditions to afford the corresponding 1,2,3-triazoles in good yields (Table 1, entries 12, and 14–17). The ratio of 1,4- to 1,5-isomers ranging from 57:43 to 100:0 indicated 1,4-disubstituted regioselectivity of the reaction was raised with the increase of the carbon chain length in primary aliphatic bromides. Unfortunately, disubstituted acetylene, such as diphenylacetylene could not react with sodium azide and benzyl chloride under the optimized reaction conditions. Bifunctional organic halides, such as, *p*-(CH₂Cl)C₆H₄CH₂Cl and CH₂BrCH₂Br, also reacted with two equivalents of sodium azide and phenylacetylene to generate the desired bis-1,2,3-triazoles in 81% and 65% yields with the ratio of 1,4- versus 1,5-isomers 100:0 and 51:49 respectively (Table 1, entries 8 and 19). This regioselectivity is the same as their corresponding mono-functional benzyl chloride or *n*-butyl bromide.

In 2003, Leadbeater reported the transition-metal free Suzuki coupling reaction [18b,18c] and Sonogashira-type coupling under microwave irradiation conditions [18a]. Two years later, after delicate analysis the microamount palladium in the reaction mixtures, including ultrapure water and commercially available sodium carbonate by ICP-MS, Leadbeater found that, although the reaction can be run without the need for addition of a transition-metal catalyst, palladium contaminants down to a level of 50 ppb found in commercially available sodium carbonate are responsible for the generation of the biaryl rather than, as previously suggested, an alternative non-palladium-mediated pathway [26]. Inspired by their results, we must therefore investigate how much copper is present in alkyl halide, sodium azide, alkyne and water in our reaction system in order to establish whether this process is only catalyzed by a microamount copper or not. We analyzed the alkyl halide, sodium azide, alkyne and water used in the reaction by ICP-MS and found that the copper level was 2.54, 4.57, 3.78, and 1.88 ppb, respectively, which we believe to be too low to be catalytically active. The organic reagents and water used in



Scheme 1.

Table 1. One-Pot Synthesis of 1,2,3-Triazoles from Alkyl Halides, NaN₃, and Alkynes^a

Entry	RX	RC≡CH	Yield [%] ^b	1,2,3-Triazole 1,4-isomer : 1,5-isomer
1	C ₆ H ₅ CH ₂ Cl	C ₆ H ₅ C CH	95 88 ^c 15 ^d	100 : 0 62 : 38 46 : 54
2	C ₆ H ₅ CH ₂ Br	C ₆ H ₅ C CH	94	100 : 0
3	C ₆ H ₅ CH ₂ Cl	<i>p</i> -CH ₃ C ₆ H ₄ C CH	93	100 : 0
4	C ₆ H ₅ CH ₂ Cl	<i>p</i> -ClC ₆ H ₄ C CH	96	100 : 0
5	C ₆ H ₅ CH ₂ Cl	<i>p</i> -BrC ₆ H ₄ C CH	92	100 : 0
6	<i>p</i> -CH ₃ C ₆ H ₄ CH ₂ Cl	C ₆ H ₅ C CH	89	100 : 0
7	<i>p</i> -NO ₂ C ₆ H ₄ CH ₂ Cl	C ₆ H ₅ C CH	99	100 : 0
8	<i>p</i> -(CH ₂ Cl)C ₆ H ₄ CH ₂ Cl	C ₆ H ₅ C CH	81	100 : 0
9	C ₆ H ₅ CH ₂ Cl	<i>n</i> -C ₈ H ₁₇ C CH	88 77 ^c	56 : 44 58 : 42
10	C ₆ H ₅ CH ₂ Cl	<i>n</i> -C ₆ H ₁₃ C CH	81	54 : 46
11	<i>n</i> -C ₄ H ₉ I	C ₆ H ₅ C CH	82 70 ^c	55 : 45 54 : 46
12	<i>n</i> -C ₄ H ₉ Br	C ₆ H ₅ C CH	62	57 : 43
13	<i>n</i> -C ₄ H ₉ Cl	C ₆ H ₅ C CH	0	N/A
14	<i>n</i> -C ₆ H ₁₃ Br	C ₆ H ₅ C CH	87	66 : 34
15	<i>n</i> -C ₈ H ₁₇ Br	C ₆ H ₅ C CH	92	73 : 27
16	<i>n</i> -C ₁₀ H ₂₁ Br	C ₆ H ₅ C CH	78	100 : 0
17	<i>n</i> -C ₁₂ H ₂₅ Br	C ₆ H ₅ C CH	87	100 : 0
18	<i>n</i> -C ₁₆ H ₃₃ Br	C ₆ H ₅ C CH	75	100 : 0
19	CH ₂ BrCH ₂ Br	C ₆ H ₅ C CH	65	51 : 49

^aAll reactions were carried out on 1.0 mmol scale; 1.0 equiv each of organic halide and alkyne were used with 1.1 equiv. of sodium azide in 3.0 mL of water at 100 °C for 24 h. ^bIsolated yields. ^cReactions were carried out in DMF at 100 °C for 24 h. ^dReactions were carried out in C₂H₅OH at 78 °C for 24 h.

the reactions were all purified prior to use and we believe them to be true. Therefore, we expected this reaction is not catalyzed by copper. However, the reaction mechanism in the absence of copper is not fully clear and a further investigation is currently underway in our laboratory.

EXPERIMENTAL SECTION

General Remarks

Mps were recorded on a WRS-2 mp apparatus and were uncorrected. All ¹H NMR spectra were recorded at 400 or 300 MHz by Bruker NMR spectrometers. Chemical shifts are given as value in ppm and referenced to tetramethylsilane (TMS) as internal standard. IR spectra were obtained by using a Nicolet NEXUS 470 spectrophotometer. Products were purified by flash chromatography on 230–400 mesh silica gel, SiO₂.

Typical Procedure for the One-Pot Synthesis of 1,2,3-Triazoles

Under an atmosphere of nitrogen, a two-necked round-bottom flask containing a stir bar was charged with an organic halide (1.00 mmol), sodium azide (1.10 mmol), and terminal alkyne (1.00 mmol), and water (3.0 mL). The mixture was heated and stirred at 100 °C for 24 h. After cooling to room temperature, ethyl ether (2×4 mL) was added to the mixture to extract the product. The combined organic layers were washed with water and brine, dried with MgSO₄ and evaporated under reduced pressure. The residue was finally purified by flash chromatography on silica gel to give the desired product.

CONCLUSION

In conclusion, an efficient, green and safe method for the preparation of 1,2,3-triazoles directly from a variety of

benzyl and alkyl halides, sodium azide, and terminal alkynes in water under transition-metal-catalyst free reaction conditions has been developed. The reactions of terminal arylalkynes, benzyl halides and sodium azide generated the regioselective 1,4-disubstituted triazoles in excellent yields, but terminal aliphatic alkynes afforded the mixture of regioisomers (1,4-disubstituted and 1,5-disubstituted triazoles). For the reactions of primary aliphatic bromides, sodium azide and phenylacetylene, the ratio of 1,4- to 1,5-isomers ranging from 57 : 43 to 100 : 0 indicated 1,4-disubstituted regioselectivity of the reaction was raised with the increase of the carbon chain in primary aliphatic bromides. The present procedure does not require isolation of the azide intermediates and may prove to be especially useful when unstable low-molecular weight and polyvalent azides are needed. Furthermore, it is an ideal environmental benign reaction system only using water as solvent without any catalysts and additives.

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