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Sodium hydride-mediated synthesis of 1,5-diaryl-1,2,3-triazoles from *anti*-3-aryl-2,3-dibromopropanoic acids and organic azides

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ABSTRACT

A series of 1,5-disubstituted 1,2,3-triazoles are synthesized by a one-pot process from *anti*-3-aryl-2,3-dibromopropanoic acids and organic azides mediated by sodium hydride in dimethyl sulfoxide. The reaction is mild and simple, does not require a transition-metal catalyst, and gives products in good to excellent yields.

1. Introduction

1,2,3-Triazoles are attractive compounds because of their unique chemical properties and structures that find many applications in medical [1], material [2], and biological research [3]. The use of 1,2,3-triazole moieties as catalysts and ligands in transition-metal catalysis systems is also emerging [4]. The rapidly increasing number of requirements for the synthesis of these heterocycles has led to a need to develop effective methods for the preparation of diverse 1,2,3-triazole derivatives.

Copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) is an important advancement in the chemistry of 1,2,3-triazoles [5]. However, the CuAAC process works only with terminal alkynes and produces various kinds of 1,4-disubstituted 1,2,3-triazoles. In contrast to 1,4-disubstituted 1,2,3-triazoles, general and regioselective routes leading to 1,5-regioisomers are not as well developed. Among the available methods are the reactions of stabilized phosphonium ylides [6] or enamines [7] with aryl azides, the nucleophilic attack of acetylide on the electrophilic terminal nitrogen of the azide [8,9], and ruthenium-catalyzed azide–alkyne cycloaddition [10]. However, these methods have limitations that cannot be neglected.

In this paper, we report a mild and simple method for the generation of 1,5-disubstituted triazoles from readily available *anti*-3-aryl-2,3-dibromopropanoic acids and organic azides mediated by sodium hydride (Scheme 1). In this reaction, the *anti*-3-aryl-2,3-dibromopropanoic acids serve as precursors of reactive acetylides, which readily react with organic azides. The result is the exclusive formation of 1,5-disubstituted triazoles in a one-pot process. To verify the final products are 1,5-diaryl-1,2,3-triazoles, not the 1,4-isomers, we compare the ^{1}H NMR and ^{13}C NMR spectra of the final products (for details see the Supporting information) with the standard spectra in the existing literature [6–10].

2. Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker AM-400 spectrometer in $CDCl_3$ with TMS as an internal standard. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF 254 silica gel coated plates. Column chromatography was carried out using 300–400 mesh silica gel at medium pressure. The synthesis of *anti*-3-aryl-2,3-dibromopropanic acids **1** and organic azides **2** was achieved according to literature procedures [11,12]. (**CAUTION!** Aryl azides are poisonous and potentially explosive when subjected to heat, light, and pressure. Any azide synthesized should be stored below 0 °C in the dark.)

2.1. 1,5-Disubstituted 1,2,3-triazoles (*3a*)

A solution of *anti*-3-aryl-2,3-dibromopropanic acid **1** (0.6 mmol), organic azides **2** (0.5 mmol), NaH (60 mg, 2.5 mmol), and DMSO (5 mL) were placed in a sealed tube. The mixture was

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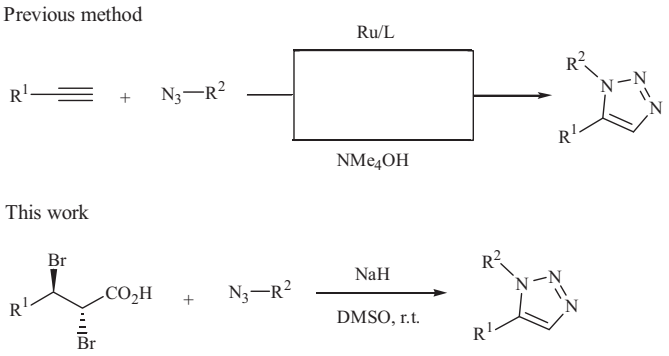
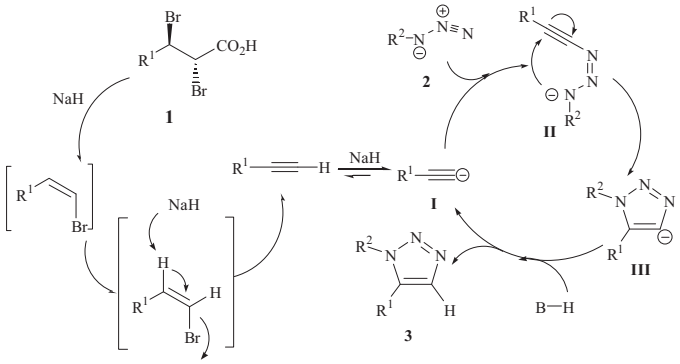


Scheme 1. One-pot synthesis of 1,5-disubstituted 1,2,3-triazoles.



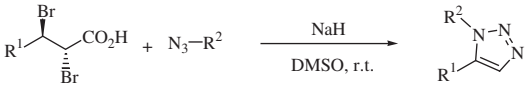
Scheme 2. Proposed mechanism of the one-pot reaction.

stirred at room temperature for 12 h. The mixture was then quenched with H_2O (25 mL). The mixture was extracted with EtOAc (3× 30 mL), and the combined organic layers were washed with brine (3× 10 mL). The extract was dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude product. Purification by column chromatography on silica gel (EtOAc–PE) afforded the desired 1,5-disubstituted-1,2,3-triazole **3a**. Yield: 100 mg (85%), yellow solid.

3. Results and discussion

The reaction was determined to proceed best using dimethylsulfoxide (DMSO) as solvent at room temperature. Then, we examined the substrate scope of the sodium hydride-mediated synthesis of 1,5-diaryl-1,2,3-triazoles (Table 1). The necessary *anti*-3-aryl-2,3-dibromopropanoic acids were easily prepared by bromination of the corresponding *trans*-α,β-unsaturated carboxylic acids [11], and the organic azides were obtained from the corresponding organic amine or organic halide [12]. As shown in Table 1, the method can be used to synthesize 1,5-diaryl-1,2,3-triazoles carrying either an electron-donating substituent (such as methyl, *tert*-butyl, or methoxy; entries 1–4) or an electron-withdrawing group (entries 5–11). Aryl azides with sterically demanding *ortho*-substituents gave slightly lower yields (entries 9 and 11). The electronic properties of both reactants also influenced the reaction outcome. Electron-deficient reactants give slightly lower yields on average than electron-rich reactants (compare entries 1–4 with entries 9–11).

Table 1
Sodium hydride-mediated synthesis of 1,4-disubstituted-1,2,3-triazoles from *anti*-3-aryl-2,3-dibromopropanoic acids and organic azides.



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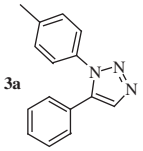
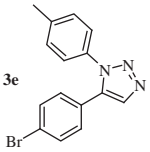
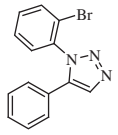
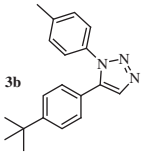
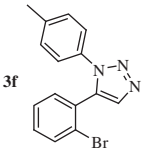
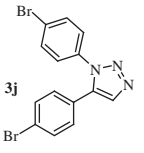
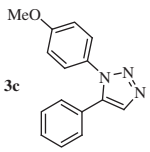
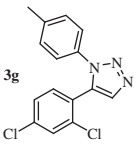
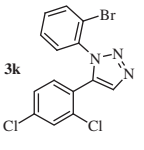
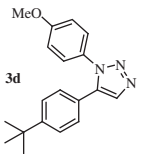
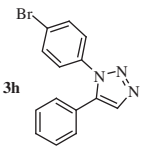
Entry[a]	Product	Yield (%)[b]	Entry[a]	Product	Yield (%)[b]	Entry[a]	Product	Yield (%)[b]
1	 **3a**	85	5	 **3e**	82	9	 **3i**	75
2	 **3b**	86	6	 **3f**	79	10	 **3j**	78
3	 **3c**	87	7	 **3g**	76	11	 **3k**	73
4	 **3d**	91	8	 **3h**	83			

[a] **1** (0.6 mmol), **2** (0.5 mmol), NaH (2.5 mmol), DMSO (5 mL), r.t., and 12 h.
[b] Isolated yield based on substrate **2**.

To study the reaction mechanism, we carried out a control experiment with *anti*-3-phenyl-2,3-dibromopropanoic acids in the absence of the azide partner and obtained the corresponding terminal alkyne in 89% yield. This finding suggested that an aralkyne was generated *in situ* in the one-pot reaction. The proposed pathway of this reaction is shown in Scheme 2, as previously described [9,13]. Initially, the *trans*-elimination reaction of *anti*-3-aryl-2,3-dibromopropanoic acid **1**, involving a simultaneous loss of carbon dioxide and bromide ions, occurs to generate the intermediate (*Z*)-β-arylvinyl bromide. A subsequent E2 *trans*-elimination gives the terminal alkyne. Reversible deprotonation of the terminal alkyne generates an aryl acetylide **I**, which acts as a nucleophile to attack the terminal nitrogen of aryl azide **2**. The triazenide intermediate **II** then undergoes either 6π-electrocyclization or 5-*endo*-dig cyclization to form 1,5-disubstituted-1,2,3-triazolyl anion **III**, which gives products **3** by the deprotonation of a DMSO molecule, terminal alkyne, or water.

4. Conclusion

We developed a simple and efficient one-pot method for the preparation of 1,5-disubstituted 1,2,3-triazoles **3** from *anti*-3-aryl-2,3-dibromopropanoic acids **1** and organic azides **2**. The reaction was mediated only by the inexpensive sodium hydride, and good to excellent yields were obtained. The process had considerable advantages in terms of readily available substrates and mild, transition-metal-free conditions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2013.05.007.

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