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Facile synthesis of bromo- and iodo-1,2,3-triazoles

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ABSTRACT

Facile synthetic routes to bromo- and iodo-1,2,3-triazoles were achieved. Diiodo-1,2,3-triazole was directly obtained from 1,2,3-triazole, and dihalo-1,2,3-triazoles were converted to halo-1,2,3-triazoles in good yields without protection by NH. Unsymmetrical 4-bromo-5-iodo-1,2,3-triazole was synthesized from bromo-1,2,3-triazole. These halo-1,2,3-triazoles can be readily prepared using common reagents and solvents and are useful building blocks for the analogous synthesis of 1,2,3-triazole derivatives.

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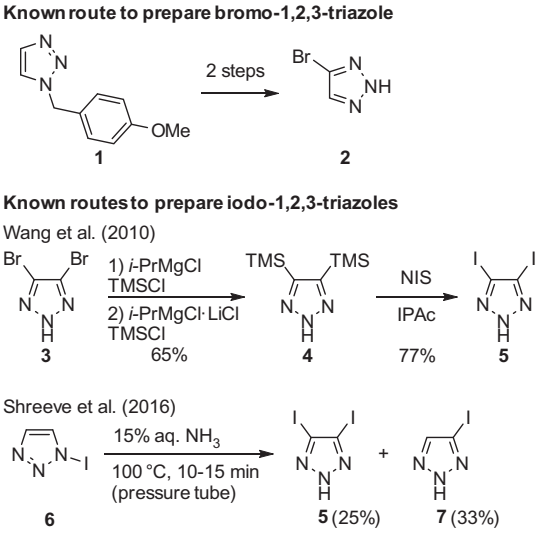
The 1,2,3-triazole moiety has been used as a heteroaryl ring in medicinal chemistry,[1] and its well-known click chemistry[2] (Huisgen reaction[3]) has expanded the many pharmacological applications of *N*-1-substituted 1,2,3-triazoles.[4] As synthons, bromo- and iodo-1,2,3-triazoles are useful building blocks for metal-catalyzed coupling reactions, such as Suzuki-Miyaura coupling.[5] To the best of our knowledge, there are few known synthetic routes to prepare bromo- and iodo-1,2,3-triazoles (Scheme 1). 4-Bromo-1,2,3-triazole (**2**) is commercially available but expensive, and its known synthetic method starting from compound **1**[6] is not efficient in terms of the atom economy. To prepare monobromo-1,2,3-triazoles from dibromo-1,2,3-triazoles, halo-metal exchange reactions were performed,[7] but the NH group of the triazole moiety must be masked. Regarding iodo-1,2,3-triazoles, direct diiodination of 1,2,3-triazole has not been reported, even though 4,5-dibromo-1,2,3-triazole (**3**) can be easily prepared by dibromination of 1,2,3-triazole.[6] Wang et al.[7b] reported that diiodo-1,2,3-triazole (**5**) was not obtained from 1,2,3-triazole using *N*-iodosuccinimide (NIS) in isopropyl acetate and that compound **5** was prepared from bis(trimethylsilyl)-1,2,3-triazole (**4**). Recently, the preparation of iodo-1,2,3-triazoles **5** and **7** was reported by Shreeve et al.,[8] but high-pressure conditions were necessary. Herein, the facile synthesis of bromo- and iodo-1,2,3-triazoles and the applications of halo-1,2,3-triazoles are discussed.

Initially, iodination of 1,2,3-triazole with NIS (1 eq.) in *N*-methyl-2-pyrrolidone (NMP) was attempted, and almost no reaction occurred at room temperature for 2 h. However, by heating the reaction mixture at 60 °C for 2 h, 4,5-diiodo-1,2,3-triazole (**5**) was observed as a major product in the LCMS data. Furthermore, running the same reaction with NIS (3 eq.) in NMP at 100 °C for 30 min resulted in good conversion to give the desired product **5**. An equimolar amount of 1,3-diiodo-5,5-dimethylhydantoin (DIH)[9] in NMP also produced compound **5** as a major product. Therefore, the two iodine atoms of DIH participated in the reaction.



Scheme 1. Known preparation methods for bromo- and iodo-1,2,3-triazoles.

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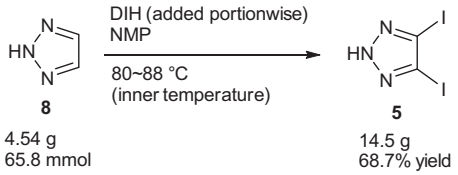


Scheme 2. Diiodination of 1,2,3-triazole.

The product was precipitated after addition of water to the reaction mixture, and the solid product was collected by filtration to afford **5** in 65% yield (0.5 mmol scale). Since the DSC (differential scanning calorimetry) data for 4-iodo-1,2,3-triazole (**7**) indicated exothermal decomposition at approximately 150 °C[8] and the diiodination was exothermal, large-scale production of this compound should be carefully conducted. A scaled-up reaction (65.8 mmol scale) was performed by adding DIH portionwise to manage the reaction temperature. As a result, the temperature of the reaction mixture was maintained within 80–88 °C, and 14.5 grams of the desired product **5** were obtained from 1,2,3-triazole (**8**) without purification by column chromatography (Scheme 2).[10]

Next, the conditions to prepare bromo- and iodo-1,2,3-triazoles (**2** and **7**) were explored. Because the halogenation of 1,2,3-triazole using one equivalent of bromine or NIS generated dihalo-1,2,3-triazole as a major product, the direct preparation of monohalo-1,2,3-triazoles **2** and **7** from 1,2,3-triazole was believed to be difficult. Therefore, we investigated the removal of one halogen atom from the dihalo-1,2,3-triazoles. 4,5-Dibromo-1,2,3-triazole (**3**) was treated with sodium sulfite[11] in water at 110 °C, and the reaction interestingly gave 4-bromo-1,2,3-triazole (**2**) without notable over-reaction (Table 1, run 1). In addition, basic and acidic conditions were examined. In the presence of K_3PO_4, no desired product was observed (run 2). The addition of acetic acid did not affect the reaction (run 3). To minimize the risk of thermal decomposition of the desired product, the hot plate was set to 100 °C, at which temperature the reaction took 3 days (run 4). For the reduction of 4,5-diiodo-1,2,3-triazole (**5**), mild conditions (80 °C for 2.5 h) produced the desired product **7** in good yield (run 5).

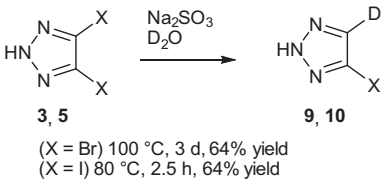
Reduction with sodium sulfite can be applied to prepare deuterated compounds that are attractive for drug discovery.[12] The reduction of dibromo- and diiodo-1,2,3-triazoles (**3** and **5**) with sodium sulfite in deuterium oxide gave the corresponding deuterated bromo- and iodo-1,2,3-triazoles (**9** and **10**) under the same conditions as for the reduction in water (Scheme 3).

Furthermore, iodination of 4-bromo-1,2,3-triazole (**2**) provided the unsymmetrical 4-bromo-5-iodo-1,2,3-triazole (**11**) which can be used for regio-selective Suzuki-Miyaura coupling reaction.[13] Compound **2** was treated with DIH in NMP at 60 °C for 2 h and the desired product **11** was obtained in a good yield (Scheme 4). The iodination of 4-bromo-1,2,3-triazole was faster than that of 1,2,3-triazole.

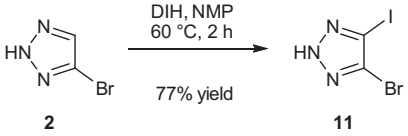
Table 1
Conditions used to prepare monohalo-1,2,3-triazoles.

Run	X	Conditions	Results
1	Br	Na_2SO_3 (3 eq.), water, 110 °C, 20 h	**3**/**2** ratio[a] = 6:94
2	Br	Na_2SO_3 (3 eq.), K_3PO_4, water, 110 °C, 20 h	No reaction
3	Br	Na_2SO_3 (3 eq.), AcOH, water, 110 °C, 17 h	**3**/**2** ratio[a] = 9:91
4	Br	Na_2SO_3 (3 eq.), water, 100 °C, 3 d	67% isolated yield
5	I	Na_2SO_3 (3 eq.), water, 80 °C, 2.5 h	72% isolated yield

[a] The ratio was calculated from the LCMS peak areas of PDA.

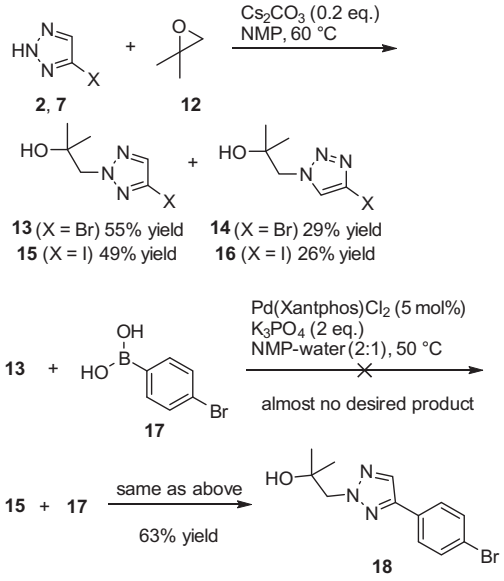


Scheme 3. Preparation of deuterated 1,2,3-triazoles.



Scheme 4. Synthesis of 4-bromo-5-iodo-1,2,3-triazole.

The applications of halo-1,2,3-triazoles are described in Scheme 5. Bromo- and iodo-1,2,3-triazoles **2** and **7** were reacted with an epoxide **12** in the presence of a catalytic amount of cesium carbonate to give *N*-1- and *N*-2-regioisomers (**13**–**16**). In general, *N*-1-substituted triazoles are more polar than *N*-2-substituted triazoles because of their different dipole moments.[6] Therefore, the regioisomers were easily isolated by column chromatography. The structures of the iodo-1,2,3-triazole analogs **15** and **16** were confirmed by HMBC experiments with **15** and **16** and the NMR spectra (^1H and ^{13}C) of the des-iodo compounds after hydrogenation.[14] Using *N*-2-substituted halo-1,2,3-triazoles **13** and **15**, Suzuki-Miyaura coupling with 4-bromophenyl boronic acid (**17**) was performed. Pd(Xantphos)Cl_2 was selected as the catalyst because it has been used for selective Suzuki-Miyaura coupling with a heteroaryl halide rather than phenylbromide.[15] The bromo-1,2,3-triazole analog **13** did not give the desired product, and the starting material **17** was consumed. This result indicated that compound **13** was less reactive than the bromophenyl analog **17**, and homocoupling reaction of **17** proceeded. Conversely, the iodo-1,2,3-triazole analog **15** was more reactive than **17**, and the reaction produced the desired product **18** in 63% yield. The sequential reactions starting from 4-iodo-1,2,3-triazole (**7**) provide a convenient strategy for the synthesis of a diverse library of 1,2,3-triazole derivatives.



Scheme 5. Applications of halo-1,2,3-triazoles.

In summary, novel approaches to prepare 4,5-diiodo-1,2,3-triazole, 4-bromo-1,2,3-triazole, 4-iodo-1,2,3-triazole, and 4-bromo-5-iodo-1,2,3-triazole have been demonstrated. The conditions of the diiodination and reduction reactions were robust and used only common reagents and solvents. Using these facile synthetic methods, halo-1,2,3-triazoles become easily accessible, expanding the synthetic strategies to produce 1,2,3-triazole derivatives.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.07.016.

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