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Base-catalyzed hydrogen–deuterium exchange and dehalogenation reactions of 1,2,3-triazole derivatives

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ABSTRACT

An efficient and convenient synthesis of deuterium-labeled 1,2,3-triazoles using base-catalysis with DMSO-d_6 as the deuterium source was developed. A series of deuterated 1,2,3-triazoles bearing various substituents were produced by hydrogen–deuterium exchange reactions of pre-synthesized original 1,2,3-triazoles, giving high level of deuteration and high yields. The catalytic system was successfully extended to the dehalogenation and halogen–deuterium exchange procedures of iodo-functionalized 1,2,3-triazolyl derivatives. This study forms a promising basis for the future development of 1,2,3-triazolyl-containing organic derivatives, polymeric materials and biomedical molecules.

1. Introduction

With the development of analytical methods for the detection of stable isotopes by NMR spectroscopy or mass spectrometry, isotopically labeled compounds have recently been recognized to be remarkably useful in many respects, including the investigation of reaction kinetics and mechanisms, structural elucidation of biological macromolecules, study of drug metabolisms, quantitative analyses of environmental pollutants and residual pesticides, and exploration of new non-linear optical materials.[1,2] In particular, the use of isotopically labeled compounds as internal standards is a key step in the investigation of samples originating from environmental, animal and human studies.[3] The rising demand for isotopically labeled compounds has led to an increased interest in the development of isotope-labeling methods. This is especially the case for the hydrogen–deuterium exchange strategy that stands as a conventional technique for the preparation of deuterium-labeled reagents. Such reactions are promoted by acids, bases, transition metals, enzymes, or microwave irradiation, and super- or sub-critical conditions.[1b,4] The applications of existing hydrogen–deuterium exchange systems are largely restricted by their high catalyst cost, low deuteration efficiency, low regioselectivity, or harsh conditions, however. Therefore the development of efficient and convenient methodologies for the synthesis of specifically deuterium-labeled compounds still remains an important and challenging task.

As a family of five-membered nitrogen-containing heterocyclic compounds, 1,2,3-triazoles have a myriad of applications in biomedical science, synthetic organic/inorganic chemistry, environmental science, and material science,[5] because 1,2,3-triazole derivatives possess many interesting features, such as antibacterial properties, *anti*-allergic properties, *anti*-HIV, antineoplastic activity, and unique coordinating behaviors to metal centers.[6] Since the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction assembling 1,4-disubstituted 1,2,3-triazoles was discovered by the groups of Sharpless[7] and Meldal[8] in 2002, the applications of 1,2,3-triazoles form a fast-growing field. In a related context, the finding of efficient and simple synthetic protocols for the synthesis of deuterium-labeled 1,2,3-triazoles would greatly promote the uses of this very large family of compounds.

Some procedures for C-5 or C-4 deuteration of 1,2,3-triazoles have been reported, as shown in Scheme 1. They include the preparations of deuterated 1,2,3-triazoles using aluminum (Scheme 1a),[9] copper (Scheme 1b),[10] magnesium (Scheme 1c)[11] or lithium (Scheme 1d)[12] intermediates. These organometallics are somewhat hazardous or sensitive to ambient atmosphere, however, which causes inconveniences for practical applications. More recently, Lakshman's group[13] reported the elegant preparation of deuterated

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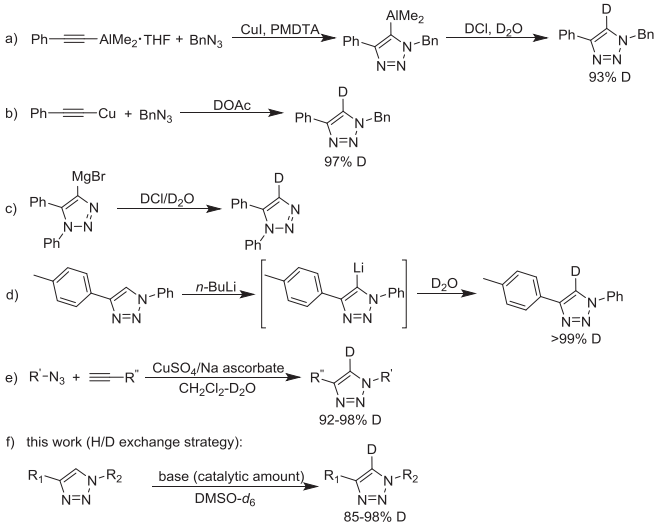
1,2,3-triazoles by $CuSO_4$/Na ascorbate-catalyzed CuAAC reaction in a biphasic CH_2Cl_2/D_2O medium (Scheme 1e).



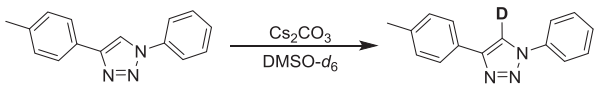
Scheme 1. Synthetic routes to deuterated 1,2,3-triazoles.

Hence, we report a general, straightforward and efficient route to deuterated 1,2,3-triazoles by means of base-catalyzed hydrogen–deuterium exchange reactions of pre-synthesized 1,4-disubstituted 1,2,3-triazoles using DMSO-d_6 as the deuterium source (Scheme 1f). Additionally, the present catalytic system is also useful in dehalogenation of 1,2,3-triazole derivatives. Contrary to the use of D_2O as a deuteration agent that is common,[14] deuteration using DMSO-d_6 is little known and has rarely been utilized,[15] although DMSO-d_6 is a common NMR solvent.

2. Results/discussion

We initially optimized the conditions of the base-catalyzed hydrogen–deuterium exchange reaction using 1,2,3-triazole **1a-*H*** as model substrates. In these preliminary experiments, hydrogen–deuterium exchange reactions were conducted over several bases in DMSO-d_6. All tested inorganic bases, including Cs_2CO_3, K_2CO_3, KOH, NaOH and K_3PO_4, work in this transformation (Table 1 and Table S1). Cs_2CO_3 exhibited a largely superior activity compared with other bases. Indeed deuterium content of 96% and isolated yield of 91% were reached with 10 mol % of Cs_2CO_3 within 4 h at 70 °C (Table 1, entry 3). Moreover, ^1H and ^2H NMR spectra indicated that the deuteration occurred at C-5 position with 100% regioselectivity. The reaction did not proceed at all when the DMSO-d_6 organic bases Et_3N and pyridine were employed (Table S1, entries 5 and 6). The uses of CH_2Cl_2/D_2O or $CHCl_3/D_2O$ instead of DMSO-d_6 offered the desired deuterated product with very low yields (Table S1, entries 7 and 8). Moreover, attempts involving decreased catalytic amounts, reduction of the reaction time, or lowering the reaction temperature provided deuteration with lower deuterium contents (Table 1, entries 2, 4 and 5).

Table 1
Optimization of the reaction conditions[a]



Entry	Base (mol %)	Temperature (°C)	Time (h)	D content (%)[b]	Yield (%)[c]
1	None	70	4	0	0
2	Cs_2CO_3 (5)	70	4	91	92
3	Cs_2CO_3 (10)	70	4	96	91
4	Cs_2CO_3 (10)	70	2	89	91
5	Cs_2CO_3 (10)	60	8	86	93

[a] The reaction was carried out with **1a-*H*** (0.15 mmol) in the presence of Cs_2CO_3 in DMSO-d_6 (0.6 mL) under a nitrogen atmosphere.
[b] The D content (%±2%) was determined by ^1H NMR spectroscopy.
[c] Isolated yield for the mixture of **1a-*H*** and **1a-*D*.**

Following the efficiency of the reaction protocol described above, the generality of this regioselective hydrogen–deuterium exchange reaction was then evaluated. First, several original 1,4-disubstituted 5-*H* 1,2,3-triazoles with various substituents at the C-4 position were examined in the presence of 10–25 mol % Cs_2CO_3. As shown in Fig. 1, phenyl moieties with electron-donating (CH_3, CH_3O) groups at the *ortho*-position were tolerated, and the corresponding deuterated products **1b-*D*** and **1c-*D*** were obtained with 95% and 98% D contents, respectively. No direct correlation could be drawn between the steric hindrance and the outcome. The reaction of **1d-*H*** smoothly proceeded, producing the desired product **1d-*D*** with 98% D content and 94% isolated yield. Moreover, an electron-withdrawing substituent such as (3-F) on the phenyl groups was also suitable (**1e-*H***), but increased both reaction temperature (95 °C) and catalytic amount (25 mol %) were required in order to obtain a satisfactory D content. This deuteration protocol was successfully extended to the substrates bearing heteroatom-containing (**1f-*H***) and long-chain aliphatic (**1g-*H***) fragments at C-4 position, and excellent D contents and yields were obtained. More importantly, this catalytic system provided a special deuteration regioselectivity toward the C-5 position of the 1,2,3-triazoles in all above-mentioned cases.

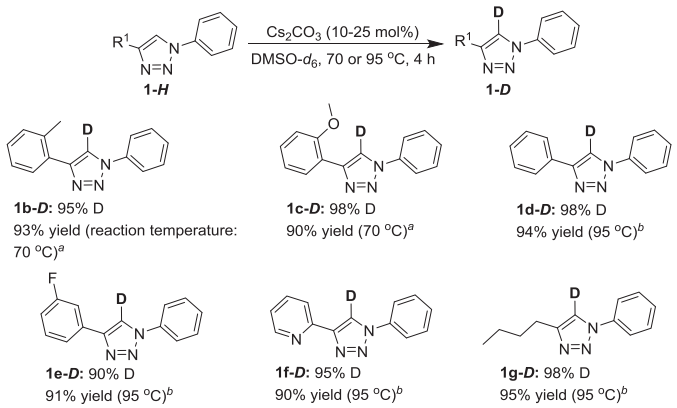


Fig. 1. Substrate scope of 1,2,3-triazoles with groups at the C-4 position; D content (%± 2%). (a) Cs_2CO_3 (10 mol %). (b) Cs_2CO_3 (25 mol %).

The scope screening of substituents at the N-1 position was then further investigated (Fig. 2). The results indicated that the presence of electron-withdrawing substituents (4-Br, 2-Br, and 4-F) on the phenyl groups caused lower hydrogen–deuterium exchange reactivity. Decreased D contents (compared to compound **1d-*D***) were detected even though reactions were carried out utilizing increased catalyst loading (50 mol %) at higher temperature (95 °C). With original 1,2,3-triazoles (**2d-*H***, **2e-*H***) containing electron-donating substituents (C_2H_5, n-C_4H_9), Cs_2CO_3 efficiently catalyzed reactions forming the corresponding deuterated triazolyl compounds **2d-*D***, **2e-*D*** with excellent D contents and yields. On the other hand, with n-C_4H_9 the D content was somewhat lower, which is probably attributable to the relative bulk in the structure. It was found that the reactions of 1,4-disubstituted 1,2,3-triazoles **2f-*H***, **2g-*H***, **2h-*H*** containing aliphatic groups proceeded smoothly, yielding the desired deuterated compounds with 93–98% D contents. In the case of **2h-*D***, a higher reaction temperature than for the other compounds of this family is required in order to obtain a high level of

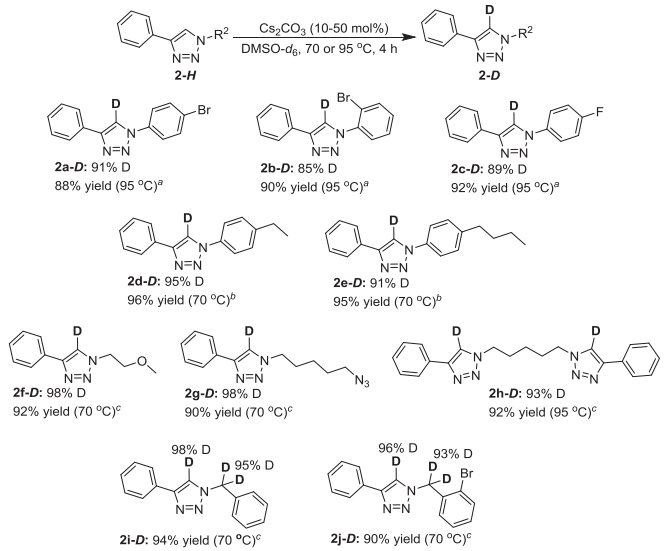
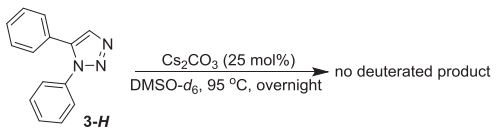


Fig. 2. Substrate scope of 1,2,3-triazoles substituted at the at N-1 position; D content (%±2%) (a) Cs_2CO_3 (50 mol %). (b) Cs_2CO_3 (10 mol %). (c) Cs_2CO_3 (25 mol %).

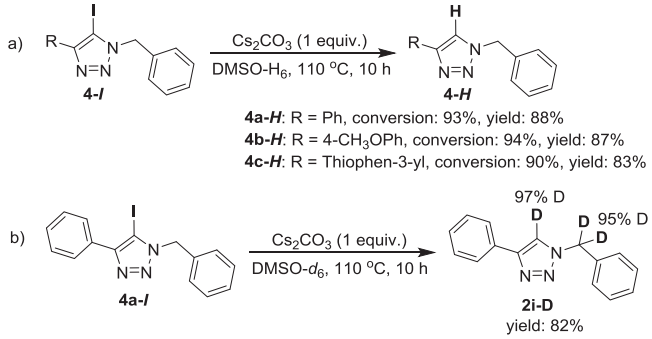
deuteration, perhaps due to its poor solubility in DMSO at lower temperature. In addition, the present procedure was also effective for the deuteration of the CH_2 group between the triazole ring and the benzene ring, and the dideuterated 1,2,3-triazole derivatives **2i-*D*** and **2j-*D*** were isolated with extremely high D contents at both C-5 and CH_2 positions. In the cases of other substrates containing juxta-cyclic CH_2 groups, such as **1g-*H***, **2d-*H***, **2e-*H***, **2f-*H***, **2g-*H*** and **2h-*H***, deuteration of these CH_2 groups did not proceed at all.

The reactivity of 1,5-disubstituted 1,2,3-triazoles was then examined to figure out whether deuteration of 1,2,3-triazole at C-4 position could occur with this protocol. No deuterated 1,2,3-triazole product was isolated, however, even with higher catalyst loading, increased reaction temperature, and prolonged reaction time (Scheme 2). The different catalytic results of 1,5-disubstituted 1,2,3-triazole from its 1,4-disubstituted counterparts might be attributed to the different electrostatic potential charges at C-4 and C-5 positions of 1,2,3-triazole[12] resulting in different acidities.



Scheme 2. Investigation of the hydrogen–deuterium exchange reaction of 1,5-disubstituted 1,2,3-triazoles.

The dehalogenation of halogeno derivatives, specifically that of aryl halides, represents an important chemical transformation in organic synthesis.[16] Dehalogenation is generally achieved using transition-metal catalysts, it would not only prevent environmental or biologic contaminate from toxic halides, but also avoid undesired further reactions caused by active halides. Moreover, dehalogenation is an efficient deuteration strategy with the assistance of deuterium sources.[17] Interestingly, it was demonstrated that the Cs_2CO_3/DMSO system also provides dehalogenation of 1,4-disubstituted 5-iodo-1,2,3-triazoles producing 1,4-disubstituted 5-*H*-1,2,3-triazoles. As shown in Scheme 3a, dehalogenation of iodo-1,2,3-triazoles (**4a-*I***, **4b-*I***, **4c-*I***) was efficient using DMSO-H_6 as solvent in the presence of 1 equiv of Cs_2CO_3, and up to 94% conversions and 88% yields. We know that 5-iodo-1,2,3-triazoles in variable amounts are usually formed as by-products when CuI is used as catalyst in azide-terminal alkyne cycloaddition,[18] probably resulting from some side reactions. This simple dehalogenation procedure using the Cs_2CO_3/DMSO system eliminates the problem. Additionally, as expected, the replacement of DMSO-H_6 by DMSO-d_6 allows the introduction of the deuterium atom at both the C-5 and methylene positions of the 1,2,3-triazoles (Scheme 3b). In the cases of substrates bearing halogen atom on the benzene ring (such as **1e-*H***, **2a-*H***, **2b-*H***, **2c-*H*** and **2j-*H***), carbon–halogen bonds survived under the recorded conditions, i.e., no dehalogenated compounds were generated.



Scheme 3. Cs_2CO_3-promoted dehalogenation reactions of 1,4-disubstituted 5-iodo-1,2,3-triazoles; halogen/deuterium exchange in **4a-*I***; D content (%±2%).

3. Conclusion

In summary, a Cs_2CO_3-catalyzed hydrogen–deuterium exchange reaction of 1,4-disubstituted 1,2,3-triazoles at C-5 position using DMSO-d_6 has been disclosed here. The high regioselectivity, good catalytic efficiency, low costs of both catalyst and deuterium source, broad substrate scope and easy-operation of this Cs_2CO_3-catalyzed procedure enable an efficient, convenient, simply and general access to deuterium-labeled 1,2,3-triazoles. In view of the remarkable importance of 1,2,3-triazolyl derivatives in many fields, this deuteration methodology could drive applications and extended studies of 1,2,3-triazoles. The present method is a very rare one using DMSO-d_6 that could be exploited and prove useful for a large number of other hydrogen–deuterium exchange reactions. It is all the more practical as DMSO-d_6 is a biocompatible solvent and reagent that is used in the same time as NMR solvent allowing to easily determine the advancement of deuteration reactions and deuterium content. In a more general context, both dehalogenation and halogen–deuterium exchange reactions have been efficiently conducted here by this means.

The presented deuteration methodology of 1,4-disubstituted 1,2,3-triazoles and the biphasic method reported earlier by Lakshman's group[13] that are both efficient are thus complementary. The former is more general than the latter, since the former is effective to pre-obtained 1,2,3-triazole compounds, regardless of synthetic routes to original 1,2,3-triazole compounds.

4. Experimental section

4.1. General remarks

All reactions were performed under nitrogen using standard Schlenk techniques, unless otherwise noted. All commercially available reagents were used as received, unless indicated otherwise. DMSO-d_6 (99.9 atom % D) was purchased from Sigma–Aldrich. Cs_2CO_3 was dried under vacuum before use. Flash column chromatography was performed using silica gel (300–400 mesh). ^1H NMR spectra were recorded using a 400 MHz spectrometer, ^{13}C NMR spectra were recorded at 100 MHz using a 400 MHz spectrometer, and ^2H NMR spectra were recorded at 62 MHz using a 400 MHz spectrometer. Almost all the original 1,4-substituted 1,2,3-triazoles were characterized by ^1H NMR using both $CDCl_3$

and DMSO-d_6 as solvents, respectively. Deuterated 1,2,3-triazole products were characterized by ^{2}H NMR using CH_2Cl_2 as solvent.

4.2. General procedure for the synthesis of original 1,4-disubstituted 1,2,3-triazoles[19,20]

A dried Schlenk tube equipped with a magnetic stir bar was charged with the alkyne (1 mmol), organic azide (1 mmol), and $Cu(PPh_3)_2NO_3$ (0.005 mmol, 3.28 mg). The mixture was stirred at rt (rt was ~25 °C) without exclusion of air under solvent-free conditions. After the reaction was completed, the mixture was diluted with ethyl acetate and filtered. The filtrate was removed under reduced pressure to obtain the crude product that was further purified by silica gel chromatography (petroleum ether/ethyl acetate (20: 1) as eluent) to yield the corresponding deuterated triazoles.

4.3. Procedure for the synthesis of original 1,5-disubstituted 1,2,3-triazole (3-*H*)[21]

To a solution of phenylacetylene (1 equiv) and azidobenzene (1 equiv) in H_2O (5 mL) was added KOH powder (0.20 equiv), then the reaction mixture was stirred at rt under N_2 to maintain a CO_2-free atmosphere. The reaction medium was quenched after 20 h by pouring the mixture into ice-cold water (50 mL). After stirring for 2 h at rt, the product **3-*H*** was isolated by vacuum filtration and dried.

4.4. General procedure for the synthesis of 1,4-disubstituted 5-iodo-1,2,3-triazoles (4-*I*)[22]

1-Iodoalkyne (0.5 mmol), azide (0.5 mmol) and $[Cu(phen)(PPh_3)_2]NO_3$ (0.015 mmol, 12 mg) were added to a flask with a stir bar, and the mixture was stirred for 36 h at rt without exclusion of air under solvent-free conditions. The reaction mixture was diluted with ethyl acetate and filtered. The filtrate was removed under reduced pressure to provide the crude product that was further purified by silica gel chromatography (petroleum ether/ethyl acetate (20: 1) as eluent) to yield the corresponding 1,4-disubstituted 5-iodo-1,2,3-triazoles.

4.5. General procedure for the synthesis of deuterated 1,2,3-triazoles (1-*D*, 2-*D*)

A dried Schlenk tube equipped with a magnetic stirring bar was charged under a nitrogen atmosphere, with pre-synthesized original 1,2,3-triazoles (0.15 mmol), Cs_2CO_3 (0.02 mmol, 6.5 mg), and DMSO-d_6 (0.5 mL). The mixture was stirred at 70 or 95 °C for 4 h. After the reaction mixture was cooled down to rt, it was diluted with CH_2Cl_2 (20 mL) and washed with H_2O and brine. The combined organic phase was dried over Na_2SO_4 and filtered. The filtrate was removed under reduced pressure to obtain the crude product that was further purified by silica gel chromatography (hexanes/ethyl acetate (20: 1) as eluent) to yield corresponding deuterated 1,2,3-triazoles.

Acknowledgements

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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.tet.2016.08.033.

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