Deuterative Cyclization of Sulfanyl 1,6-Diynes: Complete and Mono Deuteration of Functional Groups on Heterocycles

Journal:	*Organic Chemistry Frontiers*
Manuscript ID:	QO-RES-12-2014-000333.R1
Article Type:	Research Article
Date Submitted by the Author:	07-Jan-2015
Complete List of Authors:	Yoshimatsu, Mitshuiro; Gifu University, Chemistry Ito, Yukiteru; Gifu University, Chemistry

Journal Name

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ARTICLE

Deuterative Cyclization of Sulfanyl 1,6-Diynes: Complete and Mono Deuteration of Functional Groups on Heterocycles

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Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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Regioselective H/D exchange reaction of functional groups on heterocycles proceeded via a transition metal-free reductive cyclization of sulfanyl 1,6-diynes using sodium borodeuteride/ethanol-D_1. Both alkoxide− and aryloxide−mediated cyclizations and amination−cyclization resulted in the deuteration of functional groups with high deuterium incorporation. Reductive cyclization using sodium borodeuteride/ethanol exclusively afforded the monodeuterated furans and pyrroles in good yields.

1. Introduction

The H/D exchange reaction of *N*- and *O*-containing heterocycles are of considerable interest in the preparation of isotopically labeled compounds for investigating reaction mechanisms in organic chemistry and for pharmacokinetics and metabolism studies in drug development.[1] Two conceptually different methodologies have been developed for H/D exchange reactions. One methodology is pH-dependent H/D exchange reactions (classical methods) mediated or catalyzed by acids or bases.[2] As exhibited in Fig. 1, the acid- or base-catalyzed reactions deuterated through a simple autoprotic equilibrium when the reaction mixtures are heated using a conventional method (i.e., thermal and/or microwave methods); however, pH-dependent H/D exchange reactions require a large excess of the deuterium source (e.g., D_2O, D_2 or alcohol-D), long reaction times, and high reaction temperature.[3] In many cases, procedures must be repeated to achieve a high degree of deuteration (%DD).[4] Another methodology is a metal-catalyzed H/D exchange reaction, which involves comparably mild reaction conditions and is highly tolerant toward numerous functional groups.[5]

Bergman and co-workers demonstrated iridium–catalyzed H/D exchange reactions in acetone–D_6, which are suitable for the specific deuteration of aliphatic and nonfunctionalized aromatic compounds.[6] As is evident in recently reported methods using transition–metal catalysts, regioselective deuterations of the aliphatic C-H bonds on heterocycles are difficult, even when excellent C-H-activating metals, such as ruthenium,[1c,7] palladium[8], platinum[9] and rhodium are used (Fig 1).[10] Therefore, the development of facile, rapid, and efficient protocols for the deuteration of *N*-containing heterocycles would represent a substantial advancement.

We recently reported the transition-metal-free reductive cyclizations of sulfanyl 1,6-diynes using sodium borohydride in ethanol.[11] According to the reaction mechanism, the unique metal-free cyclization comprises three processes: i) the base-promoted alkyne–allene isomerization–protonation of diyne (i.e., autoprotic equilibrium); ii) the intramolecular cyclization of a bis–allene intermediate; and iii) the addition of a hydride (i.e., the nucleophilic addition of hydride). Further studies have demonstrated that the use of alcohol-D_1 instead of solvent and sodium borodeuteride instead of reducing agents, lead to the protocol for complete deuteration-cyclization of heterocycles through the base–promoted H/D exchange reactions. Furthermore, the use of a non-deuterated alcohol led to alkyne-allene isomerization and protonation to afford the mono-deuterated heterocycles by the nucleophilic addition of a deuteride. Here, we report the regioselective deuteration–cyclization of sulfanyl 1,6-diynes leading to the completely deuterated– and mono–deuterated pyrroles and furans.

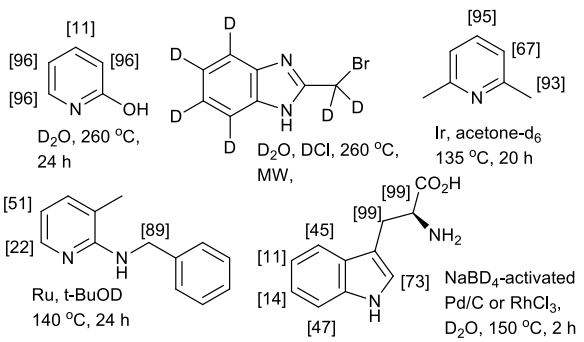

Fig 1 Deuteration of *N*-containing hetaryl compounds.

2. Results and Discussions

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† *This paper is dedicated to Professor Ei-ichi Negishi on the occation of his 80th birthday.*

‡ *Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data and ^1H and ^{13}C NMR spectra of all new compounds.*

Using our previously reported reductive cyclization conditions,[11] we examined the reductive cyclization of 1,6-diyne **1** using sodium borodeuteride (3 equiv.), DBU (3 equiv.) in ethanol-D_1 at 78 °C for 15 min (Scheme 1). Through quenching with H_2O, we obtained product **2** in 75% yield (Scheme 1). The ^{1}H NMR spectral data of **2** revealed two very small peaks assigned to methylene at δ 3.80 ppm and methyl protons at δ 1.97 ppm, which should also be observed in the ^{1}H NMR spectrum of the corresponding non-deuterated pyrrole (Fig 2). The deuterium incorporation of each proton was determined as CD_2 (92%) and CD_3 (93%) on the basis of the intensities of an external standard (1,4-dioxane). The ^{2}H NMR spectrum also showed two corresponding peaks at δ 1.98 and 3.82 ppm that were assigned to methyl and methylene groups, respectively; however, it did not show two peaks due to 2-H and 5-H on pyrrole. In the mass spectrum, five deuterium atoms were observed for **2a** obtained using this method. Furthermore, the regioselectivity of deuteration was excellent, and deuterium was selectively introduced only onto the functional groups of the pyrrole.

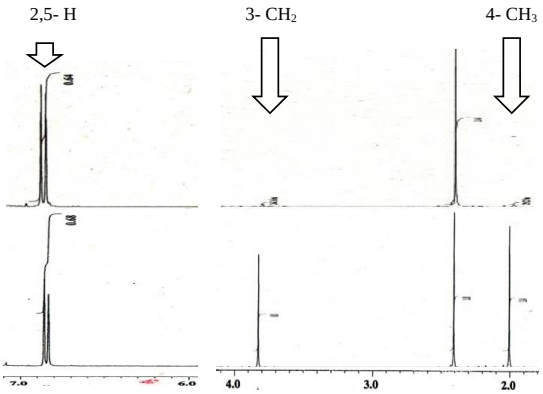
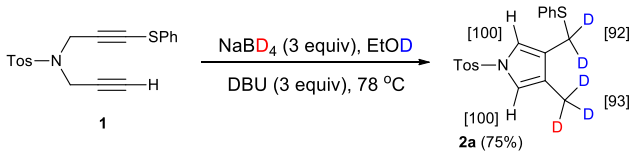


Fig 2 NMR spectral data of the compound **2a** and that of the corresponding no-deuterated compound



Scheme 1 Initial study for deuteration-cyclization

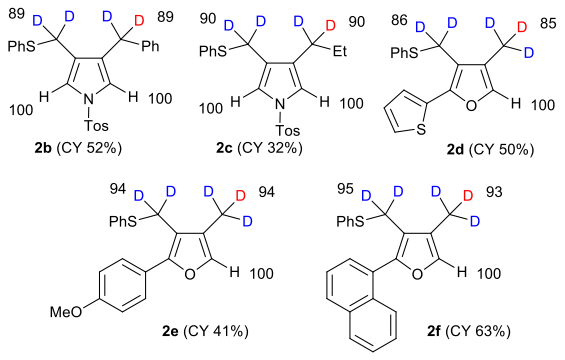
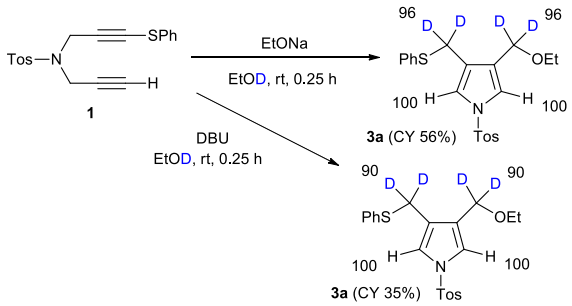


Fig 3 Scope and limitations of reductive cyclization of **1** using $NaBD_4$/EtOD

After obtaining the initial results of the unique deuterative cyclization of 1,6-diynes, we investigated the substrate scope of this reaction. Although the chemical yields of products **2b** and **2c** were moderate to low, deuterium was successfully incorporated into their functional groups. In addition, their regioselectivity was completely controlled under the experimental conditions. We also performed the deuteration–cyclization of *O*-tethered 1,6-diynes to afford the deuterated furans in 85−95 %DD (Fig 3).

Next, we focus our attention on the deuterative cyclization mediated by other nucleophiles such as alkoxides and aryloxides, which were reported a few years ago.[12] Treatment of **1** with sodium ethoxide in ethanol-D_1 at room temperature produced 4-ethoxymethylpyrrole **3a** at a 56% yield. We observed the deuterium incorporation of each proton in the ^{1}H NMR spectrum, as exhibited in Scheme 2. We observed the 96% deuterium incorporation of both the 3- and 4-methylene groups and found that the acidic pyrrole protons were not deuterated at all. In addition, we conducted a DBU-mediated cyclization reaction in ethanol-D_1. Deuterium incorporation of this product had almost the same result; however, the chemical yield was very low.



Scheme 2 Alkoxide-mediated cyclization using RONa/ROD

The results of the substrate scope of alkoxide-mediated deuterative cyclizations of 1,6-diynes are summarized in Fig 4. Sodium methoxide and ethoxide reacted with similar substrates to give pyrrole **3b** and furans **3c-d** with excellent deuterium incorporation. The reactions with aryloxide, generated in situ by treatment with sodium hydride in ethanol-D_1, also afforded aryloxymethylpyrrole **3e-g** with highly regioselective deuteration. The classical pH-dependent methods require repetitive cycles, under high thermal conditions, and long reaction times to achieve high deuterium incorporation; however, our practical protocol was observed to proceed in a single cycle, at low temperature, within 10−15 min. Furthermore, the deuteration of each substrate was exclusively regioselective.

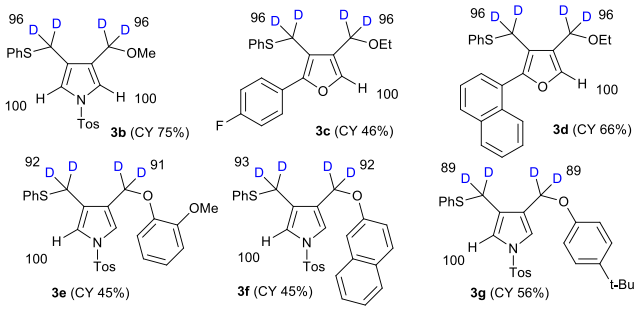
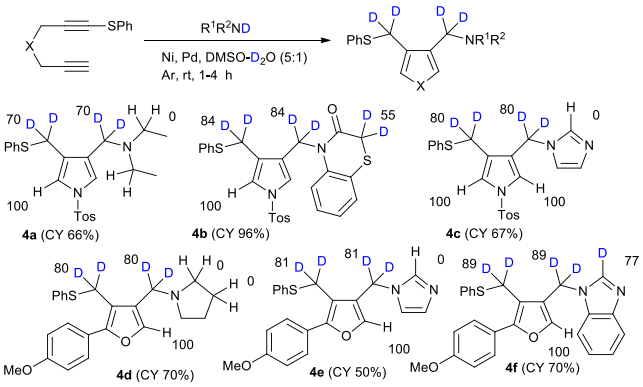


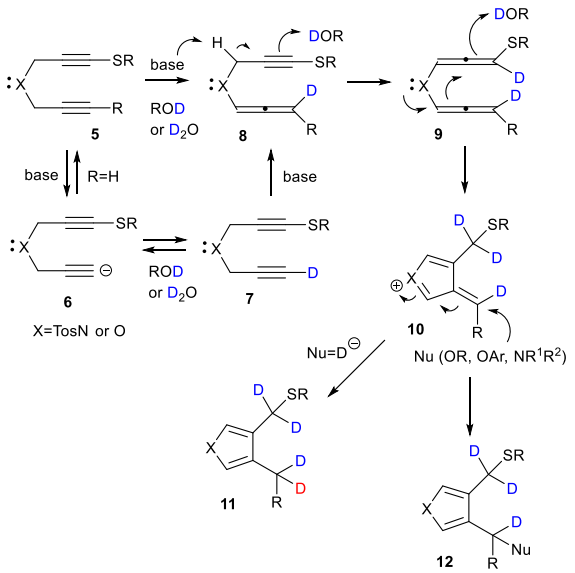
Fig 4 Scope and limitation of alkoxide-mediated cyclization

With our successful results for high deuterium incorporation into both alkoxymethyl- and aryloxymethylpyrroles and furans, we attempted the amination–cyclization of 1,6-diynes in the presence of deuterium sources.[13] The introduction of amine functional groups is an important process in drug development. On the basis of our previous work on the nickel–palladium-



Scheme 3 Amination-cyclization of 1,6-diynes with $R^1R^2ND/DMSO/D_2O$

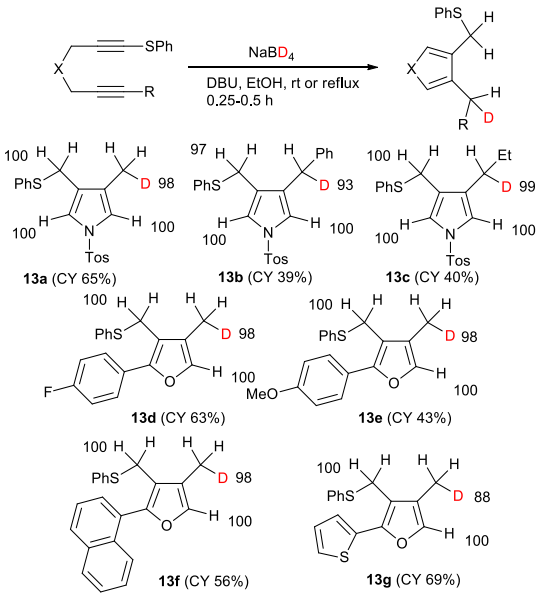
catalyzed amination–cyclization of 1,6-diynes, we conducted the reactions in this study using the secondary amine-D_1, which were prepared via the usual method involving $R^1R^2NH/NaH/D_2O$,[14] and a DMSO–D_2O mixed solvent. The reaction of **1** with diethylamine-D_1 in the presence of mixed catalysts (i.e., hexafluoroacetylacetonato nickel(II) hydrate, bis(triphenylphosphine)palladium(II) chloride) in DMSO-D_2O was examined. The regioselectivity of deuteration in the case of product **4a** was observed to be relatively high; however, the deuterium incorporation was relatively low because of water contamination of the nickel-based-catalyst. In the case of 1,4-benzothiazin-3-one, the H/D exchange reaction on the active methylene group adjacent to the sulfur atom in 55% DD was observed. In the reaction with imidazole, the H/D exchange on imidazole was not observed. The different reactivity between imidazole and benzimidazole is not clear. Similar results were obtained for furan-syntheses.



Scheme 4 Plausible reaction mechanism for deuteration-cyclization of 1,6-diynes

A plausible mechanism for the base-promoted deuterative cyclization of 1,6-diynes is presented in Scheme 4. The classical H/D exchange reaction occurs through an autoprotic equilibrium pathway under thermal or microwave conditions; however, in our system, the reaction was completed at room temperature and with a short reaction time to give the deuterated heterocycles in regioselective manner and with high deuterium incorporation because of the strong substituent effect of sulfur functional group, which facilitated alkyne-allene isomerization-deuteration. On the basis of our previous works, the sulfur-substituted 1,6-diynes should easily undergo cyclization during isomerization–protonation under basic condition via anionic **6**, monodeuterated **7**,[15] alleneyne **8** and bis(allene) **9** to give the key cationic intermediate **10**. In the reactions with sodium borodeuteride, a deuteride would attack the exo-methylene carbon of **10** to give the product-D_4 (R=Et or Ph) or –D_5 (R=D) **11**. On the other hand, the adducts–D_4 **12** (Nu=OR, OAr, NR^1R^2) was obtained in the presence of nucleophiles such as alkoxides, aryloxides and amines. Given these results, our interest turned to the mono-deuteration–cyclization of 1,6-diynes using sodium borodeuteride/ethanol.

In fact, the reaction of **1** with sodium borodeuteride in ethanol afforded the mono-deuterated pyrrole **13a** in good yield (Scheme 5). All the spectral data show that the product was regioselectively deuterated at the methyl group. Furthermore, only one deuteride was introduced and its deuterium incorporation was as high as 88%DD. The chemical yields of the reactions of both the phenyl- and ethyl-substituted 1,6-diynes were low; however, both the regioselectivities and the deuterium incorporations were excellent. Similarly, the mono-deuterated furan derivatives were obtained in good yields.



Scheme 5 Mono-deuteration-cyclization of sulfanyl 1,6-diynes with $NaBD_4$-EtOH

3. Conclusion

In summary, we have developed practical and efficient deuterative cyclization reactions of sulfanyl 1,6-diynes, leading to *N*- and *O*-containing heterocycles. Distinct from other common deuteration methods that involve autoprotic equilibrium processes or transition-metal-catalyzed C-H

activations, our complete deuteration during the formations of heterocycles proceeded reigoselectively at the functional groups of heterocycles to give the deuterated products with excellent deuterium incorporation in moderate to high chemical yields. Furthermore, the deuteration of heterocycles was not observed. Our useful protocol is also applicable to mono-deuteration–cyclization to give pyrroles-D_1 and furans-D_1, exclusively.

Experimental

Typical Procedure for Complete Deuterative Cyclization of 1,6-Diynes.

To a EtOD (1.0 mL) solution of sodium borodeuteride (17.7 mg, 0.42 mmol) and DBU (64.2 mg, 0.42 mmol) was added 4-methyl-*N*-[3-(phenylthio)-2-propyn-1-yl]-*N*-(2-propyn-1-yl)benzenesulfonamide (**1**) (50 mg, 0.14 mmol) under an Ar atomosphere. The reaction mixture was refluxed for 15 min. The cooled mixture was poured into water (50 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with AcOEt-*n*-hexane (15:1) to give 4-(methyl-d_3)-3-(phenylsulfanylmethyl-d_2)-1-(4-methylphenylsulfonyl)-*1H*-pyrrole (**2a**) (38.0 mg, 75 %) as white powders.

Typical Procedure for Monodeuteration-Cyclization of 1,6-Diyne. To a EtOH (1.0 mL) solution of DBU (64.2 mg, 0.42 mmol) and sodium borodeuteride (17.7 mg, 0.42 mmol) was added 4-methyl-*N*-[3-(phenylthio)-2-propyn-1-yl]-*N*-(2-propyn-1-yl)benzenesulfonamide (**1**) (50 mg, 0.14 mmol) under an Ar atmosphere. The reaction mixture was stirred under reflux condition for 15 min. The work-up procedure gave 4-(methyl-d_1)-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)-*1H*-pyrrole (**13a**) (33.0 mg, 65 %) as white powders.

Acknowledgements

We thank Prof. Hironao Sajiki and Prof. Yasunari Monguchi (Gifu Pharmacutical University) for their kind advice to measure ^{2}H NMR spectrum.

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