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Metal-free Reductive Cyclization and Isomerization of Sulfanyl-1,6-diynes Using Sodium Borohydride

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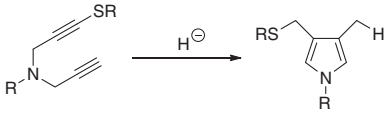
In this study, we demonstrated the metal-free reductive cyclization of sulfanyl-1,6-diynes with sodium borohydride in ethanol in the presence of diazabicyclo[5.4.0]undec-7-ene. 1,6-Diynes **1** and **5a**–**5h** bearing hydrogen or phenyl as the R^2 group afforded pyrroles **2** and **6a**–**6e** in high yields without any side reaction products such as enynyl sulfides. 1,6-Diyne (R^2 = Et) produced both pyrrole and enynyl sulfides; however, the use of cesium fluoride succeeded in the selective formation of pyrrole **6f**.

Transition-metal-catalyzed reductive cyclization of diynes and enynes is one of the most efficient methods for the construction of various five-membered rings, including heterocycles.[1] In particular, the cyclization of nitrogen-tethered 1,6-diynes is recognized as a practical method of attaining pyrrole, 2,5-dihydro-1*H*-pyrrole and 3,4-bis(methylene)-2,3,4,5-tetrahydro-1*H*-pyrrole,[2] which are found in natural products and biologically active molecules and used in material science and supramolecular chemistry.[3] Various synthetic methods for preparing highly functionalized pyrroles have been developed; however, most methods are limited by the substituent and its pattern. The Paar–Knorr synthesis for pyrrole rings is a convenient method suitable for the preparation of 2,5-dialkyl- and 2,3-dialkyl or polysubstituted pyrroles.[4] To date, much focus has been put on 2,5-unsubstituted pyrroles, which are the most important precursors for the synthesis of numerous porphyrinoid dyes and polypyrroles.[5] The previously reported methods for 2,5-unsubstituted pyrroles[6] are convenient; however, all these methods require transition metals to complete the reaction. Recently, we reported a novel method for synthesizing 3-alkoxymethyl- and 3-aminomethylfurans and -pyrroles by the functionalization–cyclization of 4-oxahepta-1,6-diynes and 4-azahepta-1,6-diynes.[7] Because this unique cyclization directly yielded 2,5-unsubstituted pyrroles, even in the absence of transition metals, we further intended to perform the metal-free cyclization of *N*-tethered 1,6-diyne with readily available reducing agents (Scheme 1). Here, we report a convenient cyclization of sulfur-substituted 1,6-diyne using sodium borohydride in ethanol.

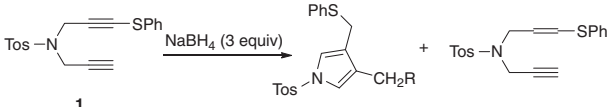
First, we performed the usual reduction using sodium borohydride in ethanol according to our previous alkoxide-mediated cyclization of 1,6-diynes.[7] Surprisingly, the reductive cyclization of **1** easily proceeded under reflux conditions to afford the desired 4-methyl-3-(phenylsulfanylmethyl)-*N*-tosylpyrrole (**2**) in 64% yield. The structure of **2** was determined based on spectral data. This revealed two types of singlet protons due to the 4-methyl group on pyrrole at δ 1.99 and the methylene group at δ 3.82 and two broad singlets due to the pyrrole ring at δ 6.83 and 6.86. Since the reductive cyclization in aprotic solvent such as THF, toluene, and 1,2-dichloroethane gave rise to a complex mixture containing desired **2** and 3,4-bis(phenylsulfanylmethyl)pyrrole, a screening of reaction conditions was performed using sodium borohydride in some alcohols (Table 1).



Scheme 1. Metal-free reductive cyclization of *N*-tethered sulfanyl 1,6-diynes.

The reaction of **1** in methanol was examined. The obtained product was not reductively cyclized pyrrole **2**, but methoxymethylpyrrole **3** (Entry 2). On the other hand, the reaction in isopropanol produced the expected pyrrole **2** in 63% yield (Entry 3). Even when the usual reducing agents such as lithium aluminum hydride, triethylsilane, and nickel borohydride were used, isolating the products was not possible. Furthermore, cyanoborohydride was not effective in the reductive cyclizations (Entry 4). Based on our experience in this field, the addition of a base has sometimes accelerated the cyclization, triggered by certain functionalizations. Therefore, we next examined reductive cyclization reactions in the presence of a base. Indeed, the use of triethylamine afforded **2** in good yield (Entry 5). Diethylamine led to the formation of vinyl sulfide **4**, which was obtained from the unexpected reduction of alkynyl sulfide (Entry 6). Other bases such as 2,2′-bipyridyl (2,2′-Py) and diazabicyclo[5.4.0]undec-7-ene (DBU) also caused the reductive cyclization of sulfanyl 1,6-diynes. Among these, DBU was

Table 1. Reductive cyclization of 1,6-diyne **1** with sodium borohydride

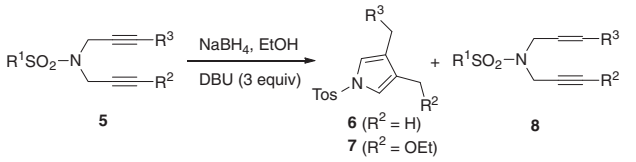


1 (Tos: *p*-toluenesulfonyl) **2** (R = H) **3** (R = OMe) **4**

Entry	Condition	Product/%	
		2 or **3**	**4**
1	EtOH, 78 °C, 0.25 h	**2** (64)	—
2	MeOH, 78 °C, 1 h	**3** (88)	—
3	*i*-PrOH, 78 °C, 10 min	**2** (63)	—
4	EtOH, 78 °C, 9 h[a]	**2** (12)	—
5	Et_3N (3 equiv), EtOH, 78 °C, 0.25 h	**2** (76)	—
6	Et_2NH (3 equiv), EtOH, 78 °C, 0.3 h	**2** (51)	**4** (49)
7	2,2′-Py (2 equiv), EtOH, 78 °C, 0.5 h	**2** (78)	—
8	DBU (3 equiv), EtOH, 78 °C, 10 min	**2** (90)	—

[a]$Na(CN)BH_3$ (3 equiv) was used.

Table 2. Reductive cyclization of 1,6-diyne **5**



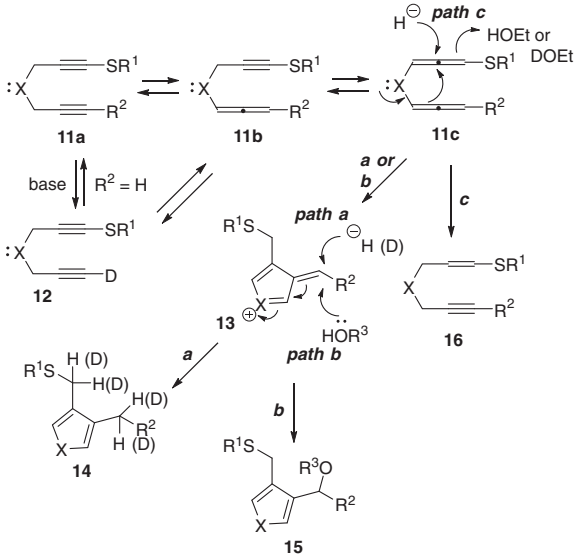
5 — 6 (R^2 = H), 7 (R^2 = OEt) — 8

Entry	R^1	R^2	R^3	Temp/°C, time/min	Product/%	
					5 or **6**	**7** and **8**
1	$MeOC_6H_4$	H	SPh	78, 10	**6a** (72)	—
2	$NO_2C_6H_4$	H	SPh	78, 5	**6b** (12)	—
3	$NO_2C_6H_4$	H	SPh	25, 120	**6b** (73)	—
4	MeC_6H_4	H	SePh	78, 13	**6c** (52)	—
5	MeC_6H_4	H	Ph	78, 90	**5d** (99)	—
6	MeC_6H_4	Ph	SPh	78, 30	**6e** (57)	—
7	MeC_6H_4	Et	SPh	78, 30	**6f** (33)	**8f** (27)[c]
8	MeC_6H_4	Et	SMe	78, 20	**6g** (20)	—
9	MeC_6H_4	Et	SAr[a]	78, 8[b]	**6h** (9)	—
10	MeC_6H_4	Et	SPh	78, 20[d]	**6f** (57)	**8f** (20)[e]

Ar = 2,4,6-triisopropylphenyl. [b]Both *i*-Pr_2NEt (3 equiv) and $NaBH_4$ (10 equiv) were used in EtOH. [c]The compound **7f** was obtained in 27% yield. [d]Reaction condition: Both CsF (3 equiv) and $NaBH_4$ (3 equiv) were used in EtOH–H_2O (1:1). [e]The compound **7f** was obtained in 17% yield.

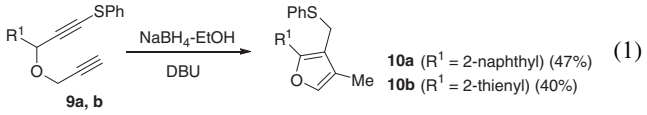
suitable for the completion of **1** with sodium borohydride reductive cyclizations (Entries 7 and 8).

We explored the scope of this reaction using the above optimal reaction conditions, as shown in Table 2. Diyne **5a**, possessing an electron-donating substituent, *p*-methoxyphenyl group, underwent reductive cyclization to give pyrrole **6a** in 72% yield (Entry 1). However, bearing an electron-withdrawing substituent, *p*-nitrophenyl group, significantly lowered the yield of pyrrole **6b** under the reflux condition (Entry 2). Our detailed research revealed that even if the reductive cyclization of **5b** using $NaBH_4$ in ethanol was performed at room temperature, it afforded 73% yield (Entry 3). The electron-withdrawing sulfonyl group effectively accelerated the reductive cyclization producing pyrroles. Phenylselanyl-1,6-diyne **5c** furnished the selanylmethylpyrrole in a similar yield as that of sulfanyl-1,6-diyne (Entry 4). Since phenyl-1,6-diyne **5d** could not participate in this reductive cyclization leading to pyrroles, to complete the cyclizations of 1,6-diynes, organosulfanyl groups must exist at the alkyne termini (Entry 5). We subsequently examined the reaction of disubstituted 1,6-diynes possessing both phenyl and ethyl groups at the alkyne termini. Although phenyl-1,6-diyne succeeded in generating pyrrole **6e**, the ethyldiyne lowered the yield of **6f** (Entries 6 and 7). We investigated the resulting mixture in detail, detecting the formation of both ethoxymethylpyrrole **7** and enyne **8**, the former was produced by alkoxylation–cyclization process and the latter was obtained by the unexpected reduction of the sulfanyl alkyne of 1,6-diyne. We further investigated the reductive cyclization of ethyl-substituted 1,6-diynes, possessing both the methanesulfanyl and bulky 2,4,6-triisopropylphenylsulfanyl R^3 groups to assess complete regioselective reductive cyclizations. The reaction of small methanesulfanyl-1,6-diyne lowered the yield of **6g** (Entry 8). On the other hand, the reaction of the bulky



Scheme 2. Proposed mechanism.

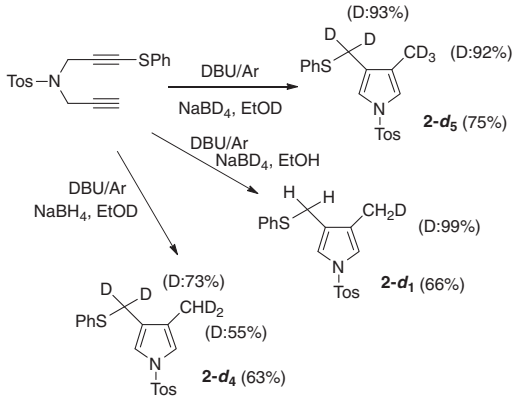
triisopropylphenylsulfanyl derivative did not proceed, but at a lower yield (Entry 9). Further investigation of the reaction condition of ethyl-substituted 1,6-diyne indicated that the weak base such as cesium fluoride significantly affected the regioselective reductive cyclization (Entry 10).



(1)

Fortunately, *O*-tethered 1,6-diynes **9a** and **9b** underwent reductive cyclization to give furan derivatives **10a** and **10b** in moderate yields (eq 1).

A possible mechanism for our metal-free reductive cyclization–isomerization of sulfanyl-1,6-diynes is shown in Scheme 2. Based on our previously reported alkoxylation–cyclizations, it is very important for this type of cyclization process to initiate the reaction by adding the base. Indeed, the addition of a base accelerated the cyclization described above. Therefore, we suggest a similar cyclization sequence to our previously reported alkoxylation–cyclization. Base-promoted alkyne–allene isomerization of **11a**–**11c** easily takes place via acetylide **12**[7,8] in the case of diyne (R^2 = H); however, disubstituted 1,6-diynes (R^2 = Ph, Et) could not. The speculation was supported by the fact that the reaction of **1** with sodium borohydride in ethanol-d_1 almost gave **2**-d_4, as shown in Scheme 3. Intramolecular cyclization of **11** affords a cationic intermediate **13**, which in a nucleophilic addition of either hydrogen or alcohols, produced either reductively cyclized **14** or alkoxylated **15** (path a or b). This was proved by the fact that the reaction of **1** with sodium borodeuteride in ethanol afforded monodeuterated pyrrole **2**-d_1 under an excellent deuterium purity. Furthermore, the reaction of **1** with $NaBD_4$ in ethanol-d_1 under an Ar atmosphere surprisingly afforded pentadeuterated pyrrole **2**-d_5 (92–93% purity) (Scheme 3). These results show that the reductive cyclization of 1,6-diynes would lead to pyrroles under a base-promoted sequential reaction: i, isomerization; ii, protonation; iii, cyclization; and iv, nucleophilic addition of hydride in

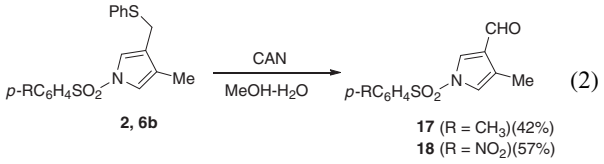


Scheme 3. Reductive cyclization with sodium borodeuteride.

alcohols. The result of Entry 5 in Table 2 indicates that the reaction of 1,6-diyne bearing no-sulfur functional group did not proceed at all. The fact is that the sulfur functional groups on the alkyne termini play a crucial role in the cyclization process (most likely because of the formation of carbanions stabilized by the organosulfur functional groups). 1,6-Diynes ($R^2 = H$) easily underwent isomerization via acetylide **12** and hydrogenation to give pyrrole **14**. However, it is very difficult to control the reaction of disubstituted 1,6-diynes because the base-promoted isomerization–cyclization of **11a** ($R^2 = Et$) to **11b** would not be easier than that of **11a** ($R^2 = H$). As a result, disubstituted 1,6-diynes ($R^2 = Et$) generated further products such as alkoxylated **15** (path b) and enynes **16** (path c).

Finally, the organosulfanylmethyl group at the alkyne termini was easily oxidized with ceric ammonium nitrate (CAN) to give the corresponding pyrrolecarboxaldehydes **17** and **18**, utilizable for further transformations (eq 2).

In summary, we reported a novel metal-free reductive cyclization reaction of sulfanyl-1,6-diynes with sodium borohydride. The reaction of *N*-tethered 1,6-diynes afforded 2,5-unsubstituted pyrroles in good yields. The CAN oxidation of the pyrrole sulfanylmethyl group generated the corresponding pyrrolecarboxaldehyde.



Supporting Information is available electronically on J-STAGE.

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