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Reductive sulfur extrusion reaction of 2,1,3-benzothiadiazole compounds: a new methodology using $NaBH_4/CoCl_2{\cdot}6H_2O_{(cat)}$ as the reducing system

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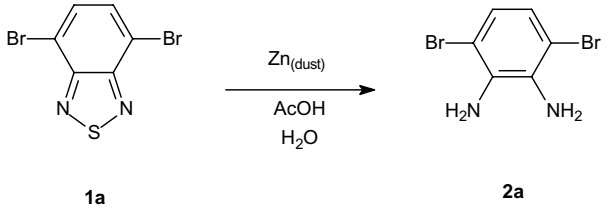
Abstract—A new simple and efficient methodology for reductive sulfur extrusion from 2,1,3-benzothiadiazole compounds has been developed using $NaBH_4$ in the presence of catalytic amounts of $CoCl_2{\cdot}6H_2O$ (1 mol %). This method is an efficient alternative for the generation of various 1,4-disubstituted-2,3-diaminobenzene derivatives from 4,7-disubstituted-2,1,3-benzothiadiazoles. The diamines can be easily converted into 4,7-disubstituted-quinoxaline compounds by simple reaction with glyoxal–sodium bisulfite.

2,1,3-Benzothiadiazole systems are among the most important nuclei in the chemistry of luminescent compounds.[1] They are also important intermediates for the preparation of quinoxaline derivatives,[2] which have a widespread use in the synthesis of photoluminescent compounds[3] and as potent adenosine receptor antagonists.[4] Various synthetic protocols are available for the synthesis of quinoxalines,[5] but sulfur extrusion from 2,1,3-benzothiadiazole systems, followed by cyclization with an appropriate 1,2-dicarbonyl compound, is a straightforward method.[2,6] Among the various reagents suitable for performing the sulfur extrusion, $LiAlH_4$[7] is one of the most used, despite the fact that it usually requires drastic reaction conditions and is limited in scope to benzothiadiazoles with non-reducible substituents. As part of our interest in new luminescent compounds[8] and in the synthesis of new quinoxaline compounds, there was a need for a simple and practical methodology for performing reductive sulfur extrusion in 2,1,3-benzothiadiazole systems. We report here that sulfur extrusion from 2,1,3-benzothiadiazole derivatives can be easily accomplished by reduction with $NaBH_4$ in the presence of catalytic amounts of $CoCl_2{\cdot}6H_2O$.

In order to prepare the diamine **2a**, necessary for the synthesis of a desired quinoxaline derivative, we initially attempted a published protocol[2a] (Scheme 1) for reductive sulfur extrusion from 4,7-dibromo-2,1,3-benzothiadiazole **1a**.[9] In our hands, **2a** was obtained in only 33% yield after the requisite crystallization.

As an alternative to this method, we tried Corey's aluminum amalgam method, used successfully for the preparation of 1,2-diphenyl-1,2-diaminoethane,[10] but not yet tested for reductive sulfur extrusion in 2,1,3-benzothiadiazole systems, hoping that Al/Hg might act as a sulfur scavenger. Indeed, treatment of **1a** with Hg_2Cl_2 and aluminum gave ^1H NMR pure **2a** in 87% yield.



1a **2a**

Scheme 1. Sulfur extrusion reaction reported by Naef and Balli.[2a]

Keywords: Sulfur extrusion; Benzothiadiazole.
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Table 1. $NaBH_4$ reduction of **1a** in the presence of catalytic amounts of $CoCl_2{\cdot}6H_2O$ to yield diamine **2a**

Entry	$CoCl_2{\cdot}6H_2O$ (mol %)	Reaction time (h)[a]	Yield (%)
1	—	3	5–8
2	—	30	81
3	1	1	81
4	2	1	77
5	3	1	78
6	4	1	71
7	5	1	70
8	10	1	54
9	1	2	90
10	1	3	97
11	1	4	96
12	1	5	94
13	1	6	94

[a] Reactions carried out in ethanol at reflux temperature.

However, the yield of this procedure was scale dependent, being high only on the 1 mmol scale.

Finally, we employed the catalytic reductive system $NaBH_4/CoCl_2{\cdot}6H_2O_{(cat)}$ in EtOH, which has been utilized[11] for the reduction of functional groups such as amides, nitriles and olefins that are inert to sodium borohydride alone. This proved to be an efficient synthetic protocol for the sulfur extrusion reaction of **1a**. The optimization of the reaction conditions for the reduction of 2,1,3-benzothiadiazole **1a** is summarized in Table 1.

As described by Ganem et al.,[11a] following the addition of $CoCl_2{\cdot}6H_2O$, the evolution of molecular hydrogen can be observed. An air-stable, granular black solid (Co_2B) precipitate,[11c] and, around 2 min later, evolution of H_2S can be noted. The reaction of 4,7-dibromo-2,1,3-benzothiadiazole **1a** and sodium borohydride in EtOH (the blank reaction), followed by ^1H NMR, produced very little product, even after 3 h at the reflux temperature (Table 1, entry 1). Although the reaction carried out at the reflux temperature produced the desired diamine in 81% yield after 30 h (entry 2), the same yield was obtained in 1 h with cobalt boride formed in situ (entry 3). Upon increasing the Co concentration from 2 to 10 mol % (entries 4–8), the isolated yield diminishes, but the conversion remains similar. This reduction in yield is probably associated with the purification process, since the extraction becomes less efficient and the product may remain adsorbed onto the black granular precipitate (Co_2B). Nitriles have been reported to be strongly adsorbed onto the granular black solid surface.[11a] Similar difficulties have been reported for primary amides,[12] but such adsorption has not been reported for amines. Entries 9–13 indicate that the optimal reaction time for completion of the reductive sulfur extrusion is 3 h.

Under optimal conditions, the reaction of **1a** with the heterogeneous catalytic system $NaBH_4/CoCl_2{\cdot}6H_2O$/EtOH produced the desired aromatic diamine **2a** in 97% yield. The purification process can be conveniently performed by a simple extraction with diethyl ether.

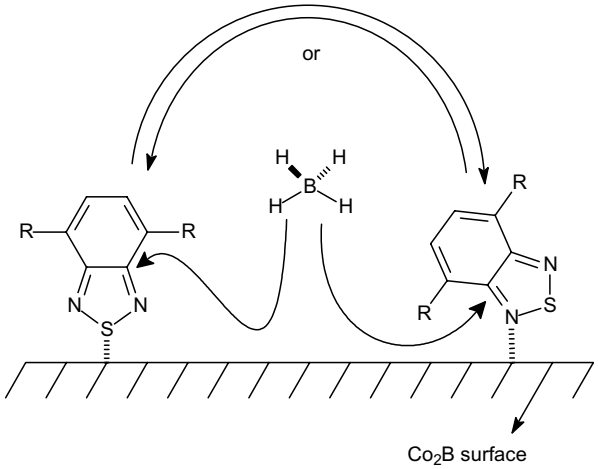


Figure 1. Proposed first step of reductive sulfur extrusion reaction of 2,1,3-benzothiadiazole compounds with $Co_2B/NaBH_4$.

The mechanism of the reductive sulfur extrusion reaction of 2,1,3-benzothiadiazoles (Fig. 1) probably follows a pathway similar to that proposed for nitrile reduction[11c] with $Co_2B/NaBH_4$.

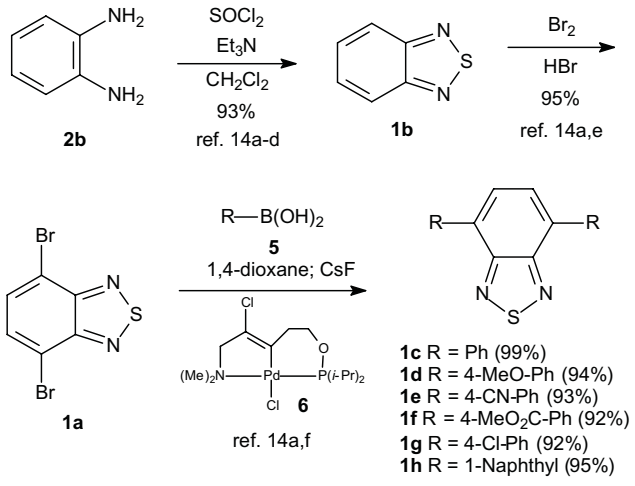
The reaction is presumably initiated by interaction between the nitrogen or sulfur atoms of the 2,1,3-thiadiazole ring and the catalyst surface (Co_2B surface). This interaction enhances the electrophilic character of the imine carbon, facilitating hydride transfer from sodium borohydride. The reduced species **3** equilibrates to species **4**, restoring the aromaticity of the six membered ring, via an imine–enamine tautomeric equilibrium, as shown in Scheme 2.

The details of the sulfur extrusion itself, which is the second step of the mechanism of the reaction, are still not clear, but the H_2S evolution suggests a hydride-mediated reductive splitting.

In order to gain insight as to the generality of this catalytic reductive sulfur extrusion reaction, it was performed on several other 2,1,3-benzothiadiazole derivatives,[13] prepared according to a procedure described elsewhere[14] (Scheme 3). The results of the reductive sulfur extrusion are summarized in Table 2.

Commercially available *o*-phenylenediamine **2b** was treated with freshly distilled thionyl chloride in the presence of triethylamine in dichloromethane as solvent,

Scheme 2. Tautomeric equilibrium imine–enamine of the reduced species.



Scheme 3. Synthetic approach to 2,1,3-benzothiadiazole **1a**–**h**.

affording 2,1,3-benzothiadiazole **1b** in 93% yield after purification by steam distillation.[14a–d] Upon reaction with molecular bromine (added dropwise very slowly) in hydrobromic acid, compound **1b** gives exclusively the 4,7-disubstituted regioisomer **1a** in 95% yield after purification.[14a,e]

The Suzuki coupling reaction of compound **1a** with the respective boronic acid, catalyzed by the NCP pincer palladacycle,[14a,f] produced the desired bis-coupled π-extended 4,7-diarylsubstituted 2,1,3-benzothiadiazoles **1c**–**h** in excellent yields after column chromatographic purification.

All reductive reactions were carried out as described in the general procedure[13] and provided the corresponding aromatic diamines **2a**–**h** (free of sulfur) in good to excellent yields. IR, ^{1}H NMR and ^{13}C NMR (APT) data are in accord with the proposed structures. All of the diamines **2a**–**h** are very air-unstable, with the exception of the commercially available diamine **2b**. This instability is a very known fact to *o*-aromaticdiamines.[6,7]

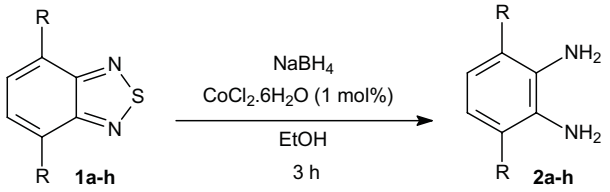
In the reaction with 2,1,3-benzothiadiazoles **1e** and **1f** (Table 2, entries 5 and 6), partial reduction of the CN and CO_2Me groups present in the molecules was observed. However, the sulfur extrusion reaction is faster than the reduction of the CN or the CO_2Me groups, so that the major product is that with the intact CN or CO_2Me groups.

Substituents on the 2,1,3-benzothiadiazole nucleus do not appear to exert an important influence on the sulfur extrusion process, since similar results were obtained with electron donating or electron withdrawing groups attached to the 2,1,3-benzothiadiazole moiety. Steric hindrance does, however, play a role. When the R group attached to the 2,1,3-benzothiadiazole nucleus is 1-naphthyl (Table 2, entry 8), the final reaction yield is only 71%, while in all other cases (Table 2, entries 1–7) the yields were consistently above 82%. The size of the 1-naphthyl group probably affects the approximation of the 2,1,3-benzothiadiazole nucleus **1h** to the cobalt boride surface.

The diamines **2** could be transformed in quinoxalines by reaction with an appropriate dicarbonyl compound or derivatives, such as glyoxal–sodium bisulfite.[15] Thus, the very air-unstable diamine **2a** was characterized by reaction with glyoxal–sodium bisulfite to give the air stable quinoxaline **7** (Scheme 4) in 76% yield, whose properties and spectra were in complete accord with the literature data for this compound.[16]

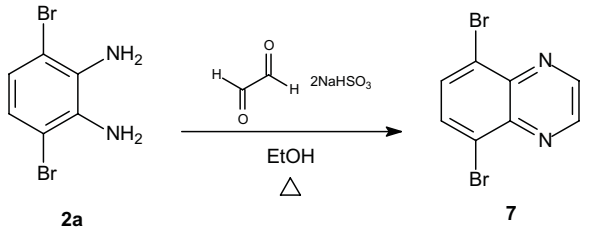
In conclusion, we describe here a novel, general, mild, fast and high yield methods for reductive sulfur extrusion from 2,1,3-benzothiadiazole compounds, utilizing the $NaBH_4/CoCl_2{\cdot}6H_2O_{(cat)}$ system in ethanol. This reduction provides a facile synthetic route to multisubstituted aromatic 1,2-diamines, key precursors for

Table 2. Catalytic reductive $NaBH_4/CoCl_2{\cdot}6H_2O$ (1 mol %) sulfur extrusion reactions



Entry	Reagent		Product		Yield (%)
	1	R	**2**	R	
1	**a**	Br	**a**	Br	97
2	**b**	H	**b**	H	95
3	**c**	Phenyl	**c**	Phenyl	91
4	**d**	4-MeO–C_6H_4	**d**	4-MeO–C_6H_4	82
5	**e**	4-NC–C_6H_4	**e**	4-H_2NCH_2–C_6H_4[a] and 4-NC–C_6H_4	88
6	**f**	4-MeO_2C–C_6H_4	**f**	4-$HOCH_2$–C_6H_4[b] and 4-MeO_2C–C_6H_4	89
7	**g**	4-Cl–C_6H_4	**g**	4-Cl–C_6H_4	91
8	**h**	1-Naphthyl	**h**	1-Naphthyl	71

[a] The CN group was partially reduced to the amine, as expected.
[b] The CO_2Me group was partially reduced to the alcohol, as expected.



Scheme 4. Cyclization of diamine **2a** to form the stable quinoxaline **7**.

the synthesis of photoluminescent compounds. In addition, like other sulfur extrusion reactions,[17] this one should also be useful in the chemistry of aromatic alkaloids.

Acknowledgements

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13. General procedure for sulfur extrusion reaction: 2,1,3-Benzothiadiazole **1** (1–10 mmol) and EtOH (150 mL, no previous solvent treatment was required) were charged into a 500 mL flask. $NaBH_4$ (1–10 mmol) was added, followed by $CoCl_2{\cdot}6H_2O$ (1 mol %). Black solid Co_2B was formed instantly and, in a few minutes, H_2S evolution was noted. The mixture was refluxed for 3 h, cooled to room temperature and then filtered to separate the black solid. The solvent was evaporated, water (100 mL) was added and the organic product was extracted with Et_2O (3×30 mL). The combined organic extracts were dried over Na_2CO_3 and the solvent removed, resulting in the very air-unstable diamine product **2**. If necessary, the product can be chromatographed on alumina (neutral), eluting with Et_2O. If the solubility of the 2,1,3-benzothiadiazole **1** in EtOH is not satisfactory, THF can be added (THF/EtOH 1:3), without appreciably affecting the results. Most of the diamines **2** must be used immediately to avoid fast decomposition.
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