



# A practical method for the reduction of 2,1,3-benzothiadiazoles to 1,2-benzenediamines with magnesium and methanol

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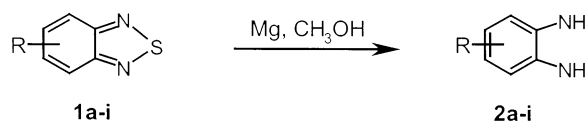
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**Abstract**—A new and practical method for the reduction of 2,1,3-benzothiadiazoles to 1,2-benzenediamines with magnesium and methanol is described. Sensitive functional groups such as bromo, chloro, cyano, and ester are well tolerated under these new conditions. © 2001 Elsevier Science Ltd. All rights reserved.

Substituted 1,2-benzenediamines are important compounds for the synthesis of agrochemical and pharmaceutical intermediates.<sup>1</sup> Because these diamines are very sensitive to a variety of reaction conditions and difficult to handle, they are often protected as 2,1,3-benzothiadiazoles.<sup>2</sup> Additionally, the resulting 2,1,3-benzothiadiazole system enables regioselective functionalization of the parent aromatic ring.<sup>3</sup> However, unraveling the diamine functionality can sometimes pose significant challenges and may be substrate dependent. Several methods have been reported in the literature for the reduction of 2,1,3-benzothiadiazoles to 1,2-benzenediamines, e.g. lithium aluminum hydride,<sup>2c</sup> Sn/HCl,<sup>4a,b</sup> SnCl<sub>2</sub>/HCl,<sup>4c</sup> sodium borohydride<sup>2a,4d,e</sup> and H<sub>2</sub>/Raney-Ni.<sup>4f</sup> All these methods have limitations. Sodium borohydride is the least reactive and reduces only electron deficient 2,1,3-benzothiadiazoles. Lithium aluminum hydride is a strong reducing agent, and heteroatoms such as bromo,<sup>5</sup> chloro,<sup>5</sup> cyano and ester groups are also reduced under these conditions. Tin is a toxic metal and is not amenable to scale-up due to safety reasons. In addition, tight specifications on toxic metals, e.g. tin, and total heavy metal content in active pharmaceutical ingredients also makes this method less desirable. Thus, we needed to develop a method for the reduction of 2,1,3-benzothiadiazoles that is safer, ecologically cleaner, and does not involve heavy metals. In this communication, we wish to report a new and practical method for the reduction of 2,1,3-benzothiadiazoles to 1,2-benzenediamines using magnesium turnings in methanol.

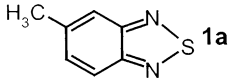
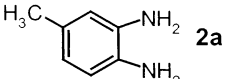
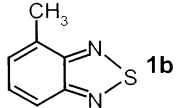
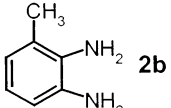
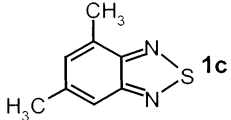
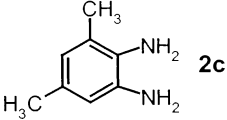
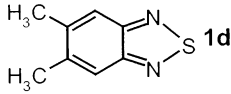
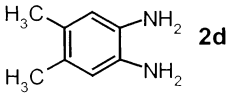
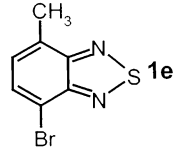
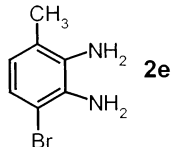
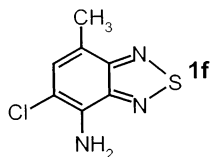
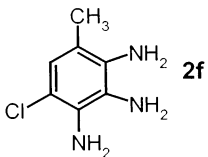
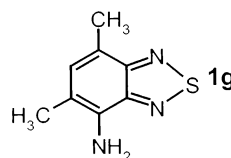
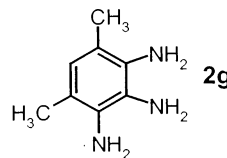
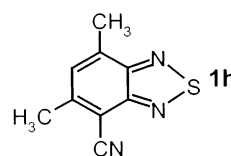
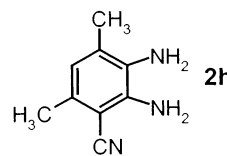
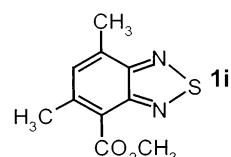
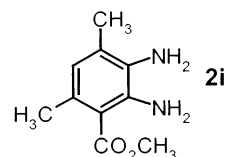
Magnesium in methanol is a known method for the reduction of  $\alpha,\beta$ -unsaturated nitriles,<sup>6a</sup> amides,<sup>6b,c</sup> and esters.<sup>6d</sup> We rationalized that this method might be suitable for the reduction of 2,1,3-benzothiadiazoles to 1,2-benzenediamines. Indeed, magnesium in methanol reduced 2,1,3-benzothiadiazoles smoothly. This method is unique in that it works only in methanol. No reduction was observed when ethanol was used as the solvent, and the starting material was recovered. Only slow destruction of magnesium metal by the solvent occurred. The exact reason for such a difference between methanol and ethanol is not understood, but solvent polarity might play an important role in this electron transfer process. The reduction of 2,1,3-benzothiadiazoles is exothermic and is carried out safely by a slow addition of magnesium turnings to a solution of the substrate in methanol which was pre-heated to 45–50°C. Several substrates containing different functional groups were successfully reduced to corresponding 1,2-benzenediamines using this method (Scheme 1), and the results are summarized in Table 1.<sup>7</sup> As is evident from entries 1–4, methyl substituted 2,1,3-benzothiadiazoles (**1a–d**) were successfully reduced in excellent yields. 7-Bromo-4-methyl-2,1,3-benzothiadiazole (**1e**) reduced exclusively to the corresponding diamine **2e** in 82% yield. Less than 2% of the debrominated product was detected. Compound **1f**, which contained a



Scheme 1.

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**Table 1.** Reduction of 2,1,3-benzothiadiazoles with Mg/methanol

Entry	Substrate	Product	Yield (%)
1	 <b>1a</b>	 <b>2a</b>	86
2	 <b>1b</b>	 <b>2b</b>	75
3	 <b>1c</b>	 <b>2c</b>	97
4	 <b>1d</b>	 <b>2d</b>	87
5	 <b>1e</b>	 <b>2e</b>	82
6	 <b>1f</b>	 <b>2f</b>	95
7	 <b>1g</b>	 <b>2g</b>	97
8	 <b>1h</b>	 <b>2h</b>	94
9	 <b>1i</b>	 <b>2i</b>	92

chlorine substituent, was also reduced satisfactorily and in excellent yield under these conditions. No dechlorinated derivative of **2f** was observed. Substrates **1g**, containing an electron-donating amino group, and **1h** and **1i**, containing an electron-withdrawing cyano or ester group, were also reduced to the corresponding triamine **2g** and diamines **2h** and **2i**, respectively, in high yields. These results clearly demonstrate the general synthetic utility of this new method.

In summary, a new and practical method for the reduction of 2,1,3-benzothiadiazoles to 1,2-benzenediamines with magnesium and methanol is described. Sensitive functional groups such as bromo, chloro, cyano, and ester are well tolerated under these conditions.

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7. **General procedure:** A four-necked, round-bottomed flask equipped with a mechanical stirrer, digital thermometer and condenser was charged with substituted 2,1,3-benzo-thiadiazole (**1a–1i**, 24.4 mmol) and methanol (80 mL). The mixture was heated to an internal temperature at 45–50°C over a period of 20 min, and magnesium turnings (194.9 mmol) were added in small portions over a period of 1 h while maintaining the internal temperature at 45–60°C. The reaction mixture was heated at 60°C for an additional 30 min. The completion of the reaction was monitored by HPLC. The mixture was concentrated under reduced pres-sure to collect ca. 50 mL of solvent. To the resulting mixture was added *t*-butylmethyl ether (160 mL). The mixture was cooled to room temperature and a saturated ammonium chloride solution (50 mL) was added. The mixture was stirred for 10 min to obtain a clear biphasic mixture, and the organic layer was separated. The aqueous layer was extracted with *t*-butylmethyl ether (50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford corresponding 1,2-benzenediamines (**2a–i**). No fur-ther purification of **2a–i** was carried out.  
Data for selected compounds **2e–i**: **2e**: mp: 54–55°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 6.87 (1H, d, *J*=8.82 Hz), 6.45 (1H, d, *J*=8.82 Hz), 3.55 (4H, bs), 2.12 (3H, s); MS (ESI): *m/z* 201.3, 203.3 (MH<sup>+</sup>). **2f**: mp: 75–76°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 6.65 (1H, s), 3.61 (2H, bs), 3.19 (4H, bs), 2.17 (3H, s); MS (ESI): *m/z* 172.1 (MH<sup>+</sup>). **2g**: mp: 110–111°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 6.45 (1H, s), 3.18 (6H, bs), 2.16 (6H, s); MS (ESI): *m/z* 152.3 (MH<sup>+</sup>). **2h**: mp: 160–162°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 6.45 (1H, s), 4.12 (2H, bs), 3.22 (2H, bs), 2.36 (3H, s), 2.16 (3H, s); MS (ESI): *m/z* 162.2 (MH<sup>+</sup>). **2i**: mp: 71–72°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 6.3 (1H, s), 3.85 (3H, s), 4.1–3.8 (4H, bs), 2.35 (3H, s), 2.15 (3H, s); MS (EI): *m/z* 194 (M<sup>+</sup>).