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A general method for the synthesis of benzimidazole-4-sulfonamides

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ABSTRACT

A general method for the synthesis of benzimidazole-4-sulfonamides is described. This methodology employs commercially available benzothiadiazole-4-sulfonyl chloride as a benzimidazole equivalent. Reaction with a variety of amines followed by highly chemoselective reductive desulfurization gives intermediate 1,2-phenylenediamines, which may then react with aryl, heteroaryl, and alkyl aldehydes to provide substituted benzimidazole sulfonamides.

The sulfonamide functional group has a long and rich history in organic chemistry and drug discovery. Beginning with the discovery of the 'sulfa' antibiotics in the 1930s that revolutionized the treatment of bacterial infections (Prontosil Rubrum, **1**), and continuing into the present day with the development of potent anti-retrovirals used to treat patients infected with HIV (Prezista, **2**), sulfonamides remain a particularly important class of compounds for the treatment of infectious diseases (Fig. 1).[1–3]

However, the use of sulfonamides as medicinal agents is not limited to the realm of infectious diseases; for example, as early as the 1950s certain sulfonamides were discovered to be effective treatments for hypertension and congestive heart failure (e.g., diuril, **3**).[1] Similarly, the benzimidazole ring system is also of long-standing medicinal importance. Examples of widely used classes of drugs containing the benzimidazole ring system include anthelmintics (albendazole, **4**) and proton pump inhibitors (omeprazole, **5**).[4,5] Additional examples of the utility of benzimidazole compounds include, among others, H_4 receptor antagonists,[6] *N*-methyl-D-aspartate receptor antagonists,[7] and hepatitis C RNA polymerase inhibitors.[8]

During the course of our investigation of cholecystokinin-2 receptor (CCK2-R) antagonists, we required benzimidazole sulfonamide **6** (Scheme 1).[9] Despite the voluminous body of literature devoted to the benzimidazole ring system, we were unable to find a straightforward method for the preparation of benzimidazole-4-sulfonamides. It is immediately apparent that the key problem is that the hypothetical reagent benzimidazole-4-sulfonyl chloride **7** does not exist due to the incompatibility of the benzimidazole nitrogen atom with sulfonyl chlorides, and to the best of our knowledge a suitable substitute has not been developed. We reasoned that commercially available 2,1,3-benzothiadiazole-4-sulfonyl chloride **8** could serve as an effective benzimidazole-2-sulfonamide synthon, and thus enable a synthesis of this class of heterocyclic compounds. Herein, we report the development of a general method for the conversion of commercially available 2,1,3-benzothiadiazole **8** into a wide variety of benzimidazole sulfonamides.

Our investigation began with the preparation of known 2,1,3-benzothiadiazoles **9**, **10**, and **11**, which represent aryl, benzyl, and alkyl-substituted sulfonamides (Scheme 2).[10] We were aware from the outset that extrusion of sulfur from 2,1,3-benzothiadiazoles typically requires the use of strong reducing agents such as $LiAlH_4$, and therefore a key challenge would be achieving chemoselectivity for the benzothiadiazole ring in the presence of the reductively labile sulfonamide group.[11]

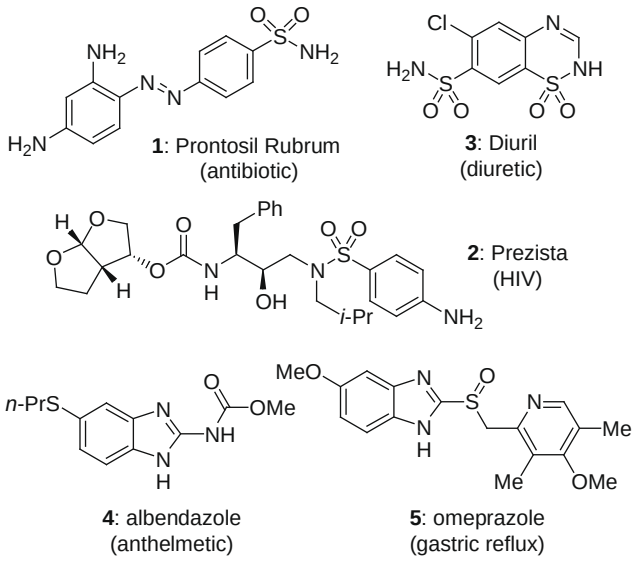

Figure 1. Drugs containing the sulfonamide or benzimidazole functional groups.

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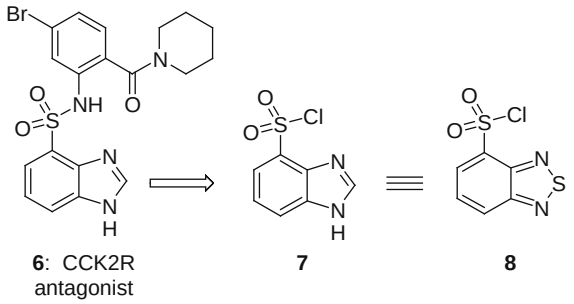
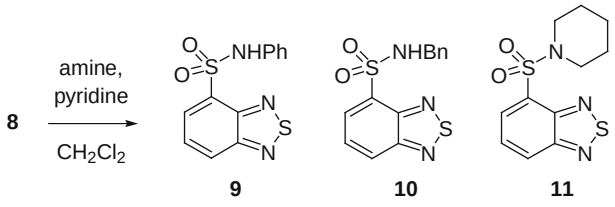


Scheme 1. Benzimidazole-4-sulfonamide CCK2-R antagonist.



Scheme 2. 2,1,3-Benzothiadiazole sulfonamide substrates.

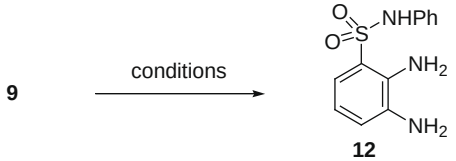
Using sulfonamide **9** as a test substrate, we surveyed various reducing agents in order to effect excision of the ring sulfur atom while leaving the sulfonamide moiety intact (Table 1). The use of $LiAlH_4$ led to both reduction of the benzothiadiazole ring and scission of the S–N bond of the sulfonamide (entry 1).[11] Treatment of **9** with magnesium turnings and refluxing methanol returned unchanged starting material (entry 2), possibly due to competitive deprotonation of the acidic sulfonamide NH proton that may render the substrate inert to reduction under these conditions.[12] The reagent combination $NaBH_4/CoCl_2$ provided the desired phenylenediamine **12** in modest yield (entry 3), although reduction of the sulfonamide N-S bond was also observed.[13] While Sn/HCl also produced **12** in modest yield, isolation of the product proved problematic due to persistent tin emulsions (entry 4). Fortunately, exposure of **9** to zinc and acetic acid at 50 °C for 1 h provided high yields of **12** (entry 5), which could be conveniently isolated as the stable hydrochloride salt in 84% yield after subsequent treatment with 4 M HCl in dioxane.[14]

Having found a reliable method for the chemoselective reduction of the 2,1,3-benzothiadiazole ring, we turned our attention to the conversion of phenylenediamine sulfonamide **12** to substituted benzimidazoles. We found that the reaction of **12** with a variety of aryl, heteroaryl, and alkyl aldehydes proceeded smoothly in the presence of $Na_2S_2O_5$ as an oxidant, providing 2-substituted benzimidazole-4-sulfonamides in yields ranging from 57% to 88% (Table 2).[15]

We next examined the cognate transformation of 2,1,3-benzothiadiazole-4-sulfonamides **10** and **11** to their corresponding benzimidazole-4-sulfonamides (Table 3). It should be noted that while **10** has three reductively labile functional groups (*N*-benzyl, sulfonamide N–S, and benzothiadiazole ring), conversion to the phenylenediamine proceeds with high chemoselectivity. Thus, reduction of **10** and **11** with zinc metal and acetic acid provided diamines **14** and **15** in yields of 76% and 80%, respectively. Oxidative condensation with aldehydes in the presence of $Na_2S_2O_5$ gave the desired benzimidazole-2-sulfonamides **16a–g** and **17a–g** in generally good yield (37–94%).

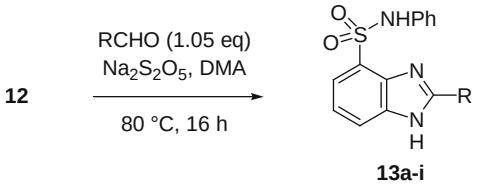
In summary, an efficient and general method for the synthesis of benzimidazole-4-sulfonamides was developed.[16,17] This methodology utilizes commercially available 2,1,3-benzothiadiazole-4-sulfonyl chloride as a benzimidazole-4-sulfonyl chloride synthon. Mild and chemoselective conditions for reduction of the benzothiadiazole ring in the presence of sulfonamide and benzyl functional groups were developed, and subsequent conversion of the intermediate

Table 1
Reduction of 2,1,3-benzothiadiazole **9** to phenylenediamine **12**



Entry	Reagents and conditions	Yield (%)
1	$LiAlH_4$, Et_2O, 23 °C	<5
2	Mg, MeOH, reflux, 16 h	<5
3	$NaBH_4/CoCl_2$, EtOH, reflux, 1 h	27
4	Sn/HCl, 50 °C, 2 h	38
5	Zn/AcOH, 50 °C, 1 h	84

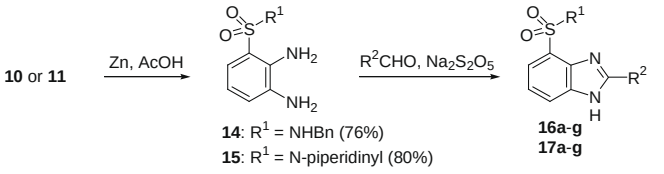
Table 2
Conversion of phenylenediamine **12** to benzimidazoles **13a–i**

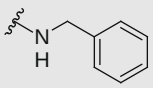
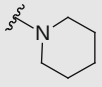


Compound	R	Yield (%)
13a	H[a]	73
13b	Ph	88
13c	3-Methoxyphenyl	52
13d	4-Methoxyphenyl	82
13e	2-Chlorophenyl	72
13f	4-Chlorophenyl	83
13g	4-Pyridyl	81
13h	*tert*-Butyl	66
13i	*n*-Pentyl	57

[a] Prepared using neat $CH(OMe)_3$, reflux, 1 h.

Table 3
Conversion of 2,1,3-benzothiadiazoles **10** and **11** to benzimidazoles **16a–g** and **17a–g**



Compound	R^1	R^2	Yield (%)
16a		Ph	79
16b		4-Methoxyphenyl	77
16c		3-Methoxyphenyl	49
16d		4-Chlorophenyl	76
16e		2-Chlorophenyl	74
16f		*tert*-Butyl	67
16g		*n*-Pentyl	70
17a		Ph	94
17b		4-Methoxyphenyl	79
17c		3-Methoxyphenyl	76
17d		4-Chlorophenyl	87
17e		2-Chlorophenyl	70
17f		*tert*-Butyl	82
17g		*n*-Pentyl	37

phenylenediamines into fully functionalized benzimidazole-4-sulfonamides was demonstrated. This methodology is tolerant of a wide variety of aryl, heteroaryl, and alkyl substitution, and is suitable for the preparation of diverse sets of benzimidazole sulfonamides.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.015.

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16. *Representative Procedure for Reduction of 2,1,3-Benzothiadiazoles-4-sulfonamides to Phenylenediamines*: 2,3-Diamino-*N*-phenyl-benzenesulfonamide hydrochloride (**12**). A mixture of 9 (1.5 g, 5.2 mmol) and AcOH (20 mL) was warmed to 50 °C with stirring, then zinc dust (1.7 g, 26 mmol) was added in portions over 10 min. The reaction mixture was stirred for 1 h, and then was allowed to cool to room temperature. The mixture was diluted with MeOH and filtered through Celite, rinsing well with MeOH, and filtrate was concentrated. The residue was partitioned between saturated aqueous $NaHCO_3$ (150 mL) and EtOAc (100 mL), and the organic phase was collected. The aqueous phase was extracted with two additional volumes of EtOAc (100 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to give 1.5 g of a crude yellow solid. This material was suspended in MeOH (15 mL) and cooled to 0 °C, then HCl (4.0 M in dioxane, 6.5 mL, 26 mmol) was added, and a green solution was obtained. This solution was concentrated, and the residue was triturated well with Et_2O to provide the hydrochloride salt **12** as a solid (1.3 g, 84%). This material was sufficiently pure to be used in the subsequent step (92-94%, HPLC). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.22 (t, J = 7.9 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 6.99 (t, J = 7.4 Hz, 1H), 6.67 (t, J = 7.9 Hz, 1H).; ^{13}C NMR (150 MHz, DMSO-d_6) δ 139.7, 137.2, 129.2, 129.1, 128.4, 123.8, 121.7, 120.3, 119.2, 115.4; MS (ESI/CI) m/z 264.1 $[MH]^+$. Anal. Calcd for $C_{12}H_{14}ClN_3O_2S$: C, 48.08; H, 4.71; N, 14.02. Found: C, 47.98; H, 5.17; N, 14.04.
17. *Representative procedure for benzimidazole formation*: 2-Phenyl-1*H*-benzimidazole-4-sulfonic acid phenylamide (**13b**). Benzaldehyde (36 μL, 0.35 mmol) was added to a mixture of **12** (0.10 g, 0.33 mmol), $Na_2S_2O_5$ (0.070 g, 0.37 mmol), and DMA (2 mL), and the mixture was stirred at 80 °C for 16 h. The mixture was allowed to cool to room temperature, then was diluted with EtOAc (25 mL) and filtered. The solution was washed sequentially with equal volumes of saturated aqueous $NaHCO_3$, water, and brine, then was dried with Na_2SO_4 and concentrated. Chromatographic purification (SiO_2, hexanes/EtOAc, 95:5 to 60:40 gradient) provided the titled compound as a solid (0.10 g, 88%). ^{1}H NMR (500 MHz, DMSO-d_6, mixture of tautomers) δ 13.30–13.55 (br s, 1H), 9.65–10.80 (br s, 1H), 8.35 (br s, 2H), 7.78 (br s, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.55–7.64 (m, 3H), 7.32 (t, J = 7.8 Hz, 1H), 7.02–7.20 (br m, 4H), 6.76–6.98 (br s, 1H); ^{13}C NMR (150 MHz, acetone-d_6, complex mixture of tautomers, shifts assignable are noted) δ 154.3 (major tautomer), 154.1 (minor tautomer), 146.6, 140.7, 139.2, 137.0, 131.6 (major tautomer), 131.5 (minor tautomer), 130.4 (major tautomer), 130.3 (minor tautomer), 130.1 (minor tautomer), 129.9 (major tautomer), 129.8 (minor tautomer), 129.6 (major tautomer), 128.1 (minor tautomer), 128.1 (major tautomer), 125.8 (minor tautomer), 125.3 (minor tautomer), 125.0 (major tautomer), 123.8 (minor tautomer), 123.1(major tautomer), 122.8 (major tautomer), 122.5 (minor tautomer), 122.0 (minor tautomer), 121.5 (major tautomer), 117.1 (major tautomer). MS (ESI) m/z 350.1 $[MH]^+$. Anal. Calcd for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.03. Found: C, 64.99; H, 4.68; N, 12.06.