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A new synthesis of 3,4-disubstituted 1,2,5-thiadiazoles

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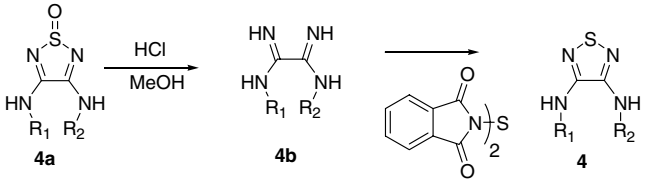
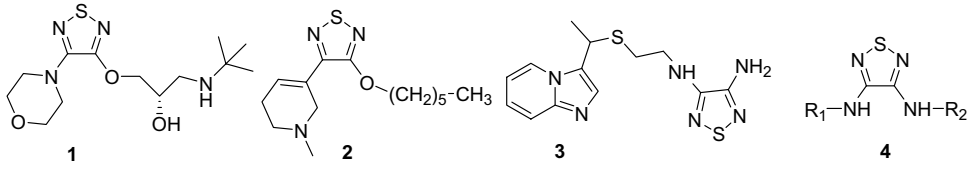
Abstract—A simple and convenient reduction of 3,4-diamino derivatives of 2,5-thiadiazole-1-oxide to the corresponding 1,2,5-thiadiazoles has been accomplished using Ph_3P and CCl_4 in dichloromethane.

3,4-Disubstituted 2,5-thiadiazoles are important heteroaryl pharmacophores in drug discovery. For example, the widely used β-adrenergic antagonist[1] Timolol® **1**, a drug for ocular hypertension, has a 3,4-disubstituted 1,2,5-thiadiazole motif. Xanomeline[2] **2** and an H-2 antagonist[3] **3**, which were in early stage clinical development, also possess the 1,2,5-thiadiazole motif. Owing to the importance of this pharmacophore in drug discovery programs in addition to our own efforts to discover a CXCR2 antagonist[4] for anti-inflammatory conditions, we became interested in the synthesis of 3,4-diamino derivatives of 1,2,5-thiadiazole **4** from readily available thiadiazole-1-oxide **4a**. Herein we report a simple synthesis of 3,4-diamino substituted 1,2,5-thiadiazoles from the corresponding thiadiazole-1-oxides through a reduction procedure using triphenyl phosphine and carbon tetrachloride.



Scheme 1. Hydrolysis route.

treatment of readily available 3,4-diethoxy thiadiazole-1-oxide **5** with various amines and alcohols, acid hydrolysis of the resulting sulfoxide **4a** results in the formation of diimine **4b**. Subsequent treatment of diimine **4b** with *N*,*N*-thiobisphthalimide generates the desired thiadiazole **4**. This Letter demonstrates a more concise approach to avoid the acid catalyzed hydrolysis of sulfoxide and



Previous reports[3,5] suggest the inability to directly reduce thiadiazole 1-oxide to thiadiazole by conventional methods. The reported synthesis of 3,4-disubstituted 1,2,5-thiadiazole requires two steps from the corresponding thiadiazole-1-oxide (Scheme 1). In general, following introduction of the 3- and 4-substituents by reintroduction of sulfur, by use of a direct reduction without ring cleavage.

The known 3,4-diethoxy 2,5-thiadiazole-1-oxide **5** was treated with phenolic amine **6**[4a] to generate the corresponding singly substituted compound **7**. Sulfoxide **7** was again treated with the commercially available benzyl amine **8** and diisopropylethylamine in methanol to afford the corresponding diamino-thiadiazole-1-oxide **9**. At this stage, we extensively studied the reduction of diamino thiadiazole-1-oxide **9** to the corresponding thiadiazole **10** using standard reduction procedures.

Keywords: 2,5-Thiadiazole 1-oxide; 1,2,5-Thiadiazole; Triphenylphosphine and carbon tetrachloride.
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After several unsuccessful attempts, reduction was finally accomplished by treating a solution of monoxide **9** in dichloromethane with triphenylphosphine, followed by the drop-wise addition of carbon tetrachloride at 0 °C. The resulting reaction mixture was slowly warmed to room temperature and then refluxed for 3 h. The purification of the final thiadiazole was accomplished by removal of the solvent under vacuum and subsequent column chromatography or preparative thin layer chromatography using methanol and dichloromethane (1:20 ratio) to afford the desired thiadiazole **10** in 85% yield (Scheme 2).

A plausible mechanism[6] for the reaction includes the formation of the intermediate **11**, which then undergoes an elimination of chloride ion and triphenylphosphine oxide, resulting in the thiadiazole **4** (Scheme 3). Both the X-ray crystal structure and ab initio theoretical calculations have shown that thiadiazole sulfoxides are non-aromatic[7] and have pyramidal sulfur. The driving force for this reduction may be the formation of a more stable, aromatic 1,2,5-thiadiazole.

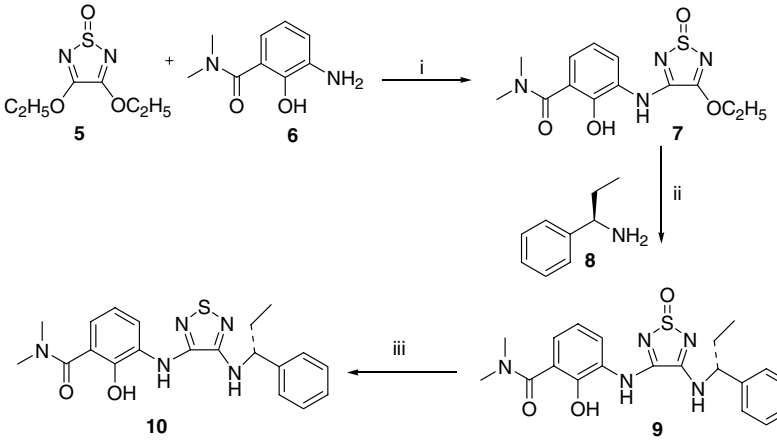
After successfully developing the reduction procedure, a number of thiadiazoles (**10a**–**h**) were synthesized in good yield as shown in Table 1. The reduction procedure is quite compatible with functional groups including amines, phenols, amides, esters, furans, and thiophenes.

The following table shows the synthesis of a variety of thiadiazoles from the corresponding thiadiazole oxides using the Ph_3P/CCl_4 reduction procedure. The monoxide intermediates (**9a** to **9h**) were prepared from the corresponding amines[4a,b] and 3,4-diethoxy 2,5-thiadiazole-1-oxide **5** in excellent yield, using the same procedure described for compound **9**. The yields for the reduction step vary from 72% to 82% in some cases.

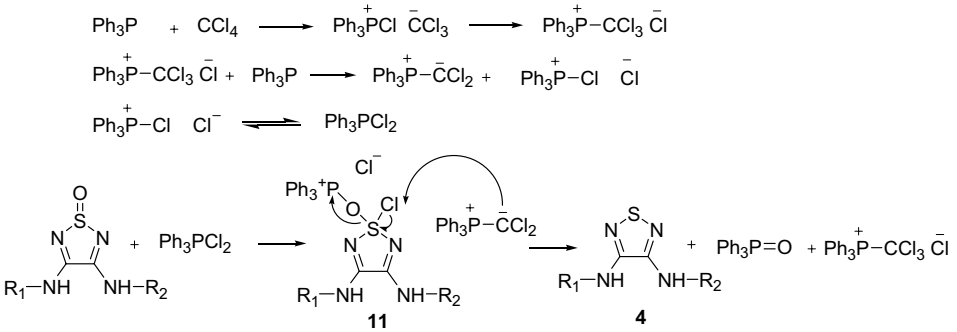
In summary, we have accomplished a simple and mild reduction of 2,5-thiadiazole-1-oxide to the corresponding 1,2,5-thiadiazole using Ph_3P and CCl_4. A plausible mechanism has been proposed and can be used for the synthesis of substituted 1,2,5-thiadiazoles in one step from the corresponding thiadiazole-1-oxide.

Spectral data: Compound **7**: ^{1}H NMR (400 MHz, DMSO-d_6): 9.58 (1H, br s), 7.64 (1H, d, $J = 8.0$ Hz), 7.04 (1H, d, $J = 7.6$ Hz), 6.92 (1H, t, $J = 8$ Hz), 4.52 (2H, m), 2.89 (6H, s), 1.42 (3H, t, $J = 7.0$ Hz): LCMS (m/z): 325.2 $(M+H)^+$, 280.2, 234.1; HRMS calcd for $C_{13}H_{17}N_4O_4S$ $(M+H)^+$: 325.09705; found: 325.09662.

Compound **9**: ^{1}H NMR (400 MHz, DMSO-d_6): 9.72 (1H, br s), 8.77 (1H, s), 7.63 (1H, d, $J = 7.6$ Hz), 7.36–7.40 (4H, m), 7.27 (1H, s), 7.01 (1H, d, $J = 7.6$ Hz), 6.91 (1H, t, $J = 7.2$ Hz), 4.77 (1H, s), 2.94 (6H, s), 1.84–1.97 (2H, m), 0.935 (3H, t, $J = 6.8$ Hz): LCMS

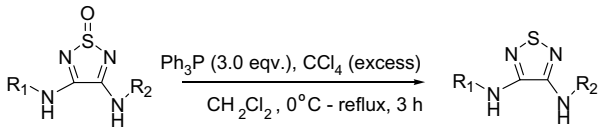


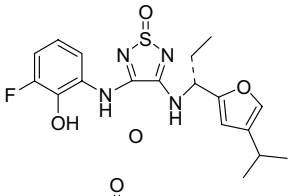
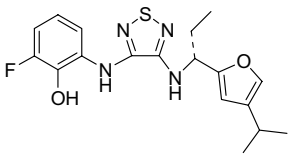
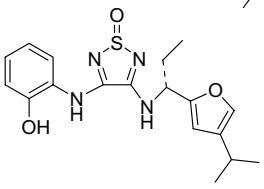
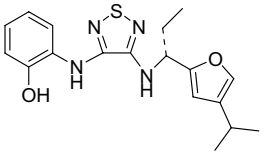
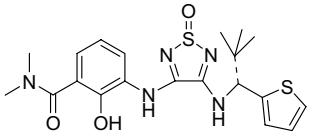
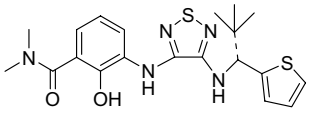
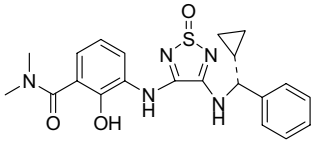
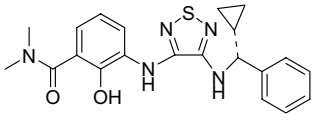
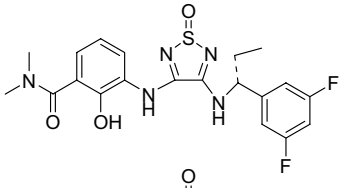
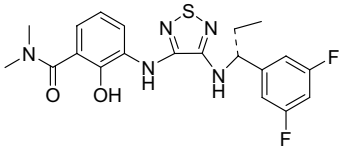
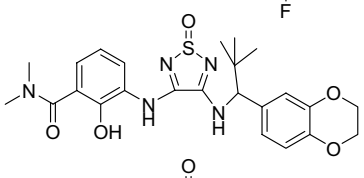
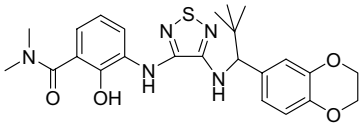
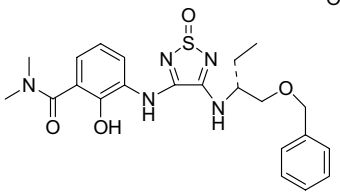
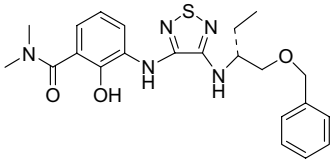
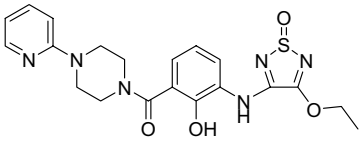
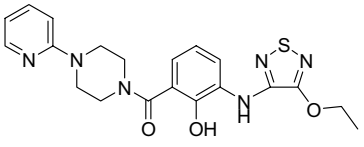
Scheme 2. Reagents and conditions: (i) diisopropylethylamine, CH_3OH, rt, 12 h, 90%; (ii) CH_3OH, diisopropylethylamine, rt, 12 h 80%; (iii) PPh_3 (3 equiv), CCl_4, CH_2Cl_2, 0 °C–reflux, 3 h; 85%.



Scheme 3. Proposed mechanism for the reduction.

Table 1. Examples of reduction of 2,5-thiadiazole-1-oxide to 1,2,5-thiadiazole



Entry	2,5-Thiadiazole-1-oxide (**9a**–**h**)		Product (**10a**–**h**) 1,2,5-thiadiazole		Yield (%)
1		**9a**		**10a**	81
2		**9b**		**10b**	78
3		**9c**		**10c**	72
4		**9d**		**10d**	81
5		**9e**		**10e**	76
6		**9f**		**10f**	78
7		**9g**		**10g**	82
8		**9h**		**10h**	78

(*m*/*z*) : 414.2 $(M+H)^+$, 351.2, 279.2, 233.1; HRMS calcd for $C_{20}H_{24}N_5O_3S$ $(M+H)^+$: 414.15998; found: 414.16200.

Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.70 (1H, s), 8.19 (1H, d, $J = 7.6$ Hz), 7.2–7.4 (5H, M), 7.16 (1H, s), 6.96 (1H d, $J = 7.2$ Hz), 6.85 (1H, t, $J = 8$ Hz), 4.74–4.84 (2H, m), 3.19 (6H, s), 2.06 (1H, m), 1.89 (1H, m), 0.95 (3H, t, $J = 7.2$ Hz): ^{13}C NMR, ($CDCl_3$): 172.0, 149.1, 147.3, 143.4, 142.6, 130.2, 128.5, 128.5, 127.3, 126.8, 126.8, 120.9, 119.4, 118.6, 116.7, 60.2, 38.5, 38.5, 29.9, 10.8; LCMS (*m*/*z*): 398.2 $(M+H)^+$, 280.2, 235.1; HRMS calcd for $C_{20}H_{24}N_5O_2S$ $(M+H)^+$: 398.16507; found: 398.16538.

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