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The ring opening of 3,4-dichloro-1,2,5-thiadiazole with metal amides. A new synthesis of 3,4-disubstituted-1,2,5-thiadiazoles

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Abstract—We have developed a new synthesis of 3,4-disubstituted-1,2,5-thiadiazoles. The methodology is based on the ring opening of readily available 3,4-dichloro-1,2,5-thiadiazole with metal amides to afford a stable synthon, which is then transformed into the 3,4-disubstituted-1,2,5-thiadiazole derivatives via two consecutive reactions with O-, S-, N- or C-nucleophiles.

Substituted 1,2,5-thiadiazole derivatives have found useful applications in many different technological areas.[1] In the pharmaceutical industry, the exceptional pharmacological properties of the 1,2,5-thiadiazole nucleus has been exploited in the development of drugs or drug candidates.[2] Therefore, the development of scalable processes for the preparation of this heterocycle has been the subject of an extensive research for many years.[3] Despite this substantial effort, most of the methods used for the synthesis of 1,2,5-thiadiazole derivatives remain difficult to scale-up because they involve the use of highly toxic (e.g., cyanogen), corrosive (e.g., S_2Cl_2) or hazardous (S_4N_4) reagents and the production of large amounts of by-products (e.g., sulfur) and wastes. On the other hand, 3,4-dichloro-1,2,5-thiadiazole **1**, a starting material in the synthesis of the Merck's β-adrenergic blocking agent Timolol, is readily available at an industrial scale but there are few examples of successful transformations of **1** into its unsymmetrical derivatives.[4] In particular, the reaction of **1** with Grignard,[5] alkyllithium[6] or metal amides[7] reagents leads mostly to ring-opened decomposition by-products through an attack on the sulfur atom. In this sense, we reported recently the synthesis of a series of alkyl-, alkenyl-, alkynyl-, aryl- and heteroaryl-1,2,5-thiadiazoles via the Pd-catalyzed cross-coupling reaction of **1** with organostannanes or -boranes.[8]

We wish to report herein a new method for the synthesis of 3,4-disubstituted-1,2,5-thiadiazoles via an unprecedented ring opening/substitution/ring closure process (Fig. 1).[9]

We found that hindered metal amides at low temperature allow to control the ring opening of **1** and to avoid the subsequent decomposition of the ring-opened products. Therefore we sought to use these latter compounds as useful unsymmetrical synthetic equivalents of **1** for the synthesis of 3,4-disubstituted-1,2,5-thiadiazoles. We initially investigated the reaction of **1** with 1 equiv of LDA in THF at −78 °C. Under these conditions, the ring-opened product **2a** was obtained in low yield (<20%) after preparative TLC separation. It appeared that LDA attacks the sulfur atom of **2a** (Fig. 2) similarly to what has been reported in the reaction of **1** with lithium (trimethylsilyl)acetylide.[7]

To avoid this side reaction, we sought to utilize more bulky and/or less nucleophilic metal amides for the ring

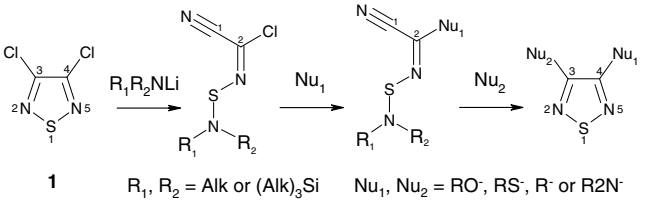

Figure 1.

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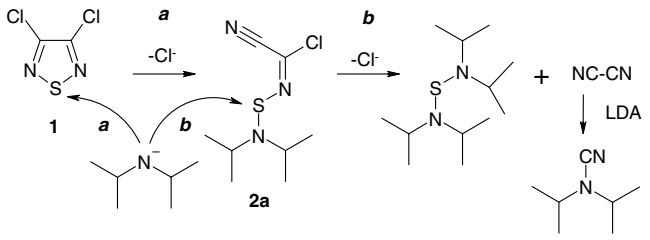


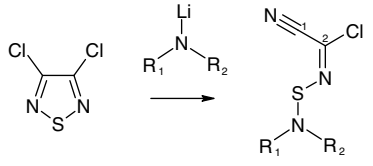
Figure 2.

opening reaction. The ring opening products **2a**–**k** were obtained by reaction of **1** with 1 equiv of lithium metal amide in solvents like methyl-*tert*-butyl ether, diethyl ether, THF or *n*-heptane (Table 1). In general, the ring opening reactions were carried out at −78 °C, but higher $T°$ (−40/−10 °C) were required for the more bulky metal amides (entries 4–6 and 10). Moderate yields were obtained with weakly hindered metal amides (entries 3, 9 and 11) due to competitive S-attack on **2c**,**2i** and **2k**.

Better results were obtained with the bis-trialkylsilyl amide derivatives (entries 2, 5 and 6) and particularly with readily available LiHMDS (entry 2). Depending on the purity of the crude reaction mixture and on the stability of the ring-opened products, we could either use them directly or after purification. It is worth mentioning that no detectable degradation of the crystalline compound **2b** has been observed after storage for several years at −20 °C.[10]

After having prepared this collection of ring-opened products, we evaluated their reactivity with O-, N-, S- and C-nucleophiles. Complete decomposition was observed with Grignard reagents, stabilized carbanions (potassium diethylmalonate) or potassium cyanide, but good yields were obtained with O-, N- and S-nucleophiles. From our initial screening study, we concluded that compounds **2b**–**d** were the more useful for synthetic purposes and we exemplified their reactivity with a series of classical nucleophiles (Table 2). As shown in Table 2, compounds **2a**–**d** reacted with a wide range of O-, N- and S-nucleophiles to afford the substitution products **3**–**6**. The tetramethylpiperidine derivative **2d** gave a high yield with all types of nucleophiles (entries 16–19). High yields were also obtained for sulfur and nitrogen nucleophiles with the bis-trimethylsilyl compound **2b** (entries 4, 5, 8–10). With alkoxides (entries 6 and 7, $PhCH_2O^- \gg Ph_2CHO^-$), we observed a competitive attack on silicon leading to the formation of cyclized products (Fig. 3). The relative reactivity order: **2c** > **2b** > **2d** was established for both O- and S-nucleophiles by the competitive substitution of these compounds with excess nucleophiles.

Table 1. Reaction of 3,4-dichloro-1,2,5-thiadiazole with metal amides



Entry	$-R_1$	$-R_2$	Experimental conditions[a]	Product (Yield %)[b]	^{13}C NMR-C^1 (ppm)	^{13}C NMR-C^2 (ppm)	IR–CN (cm^{-1})	UV–λ_{max} (nm)
1	$-CH(CH_3)_2$	$-CH(CH_3)_2$	THF or Et_2O/ −78 °C, 30 min	**2a** (20)[c]	100.3	111.5	2229	nd
2	$-Si(CH_3)_3$	$-Si(CH_3)_3$	*n*-Heptane or Et_2O/−78 °C, 30 min	**2b** (90)[d]	99.4	111.7	2227	320.8
3	$-(CH_2)_2-O-(CH_2)_2-$		*n*-Heptane or Et_2O/−78 °C, 30 min	**2c** (47)[e]	111.1	104.5	2236	294.0
4	$-C(CH_3)_2-(CH_2)_3-C(CH_3)_2-$		*t*-BuOMe/−40 °C, 20 min	**2d** (55)[e]	111.8	100.0	2225	300.8
5	$-SiCH_3(Ph)_2$	$-SiCH_3(Ph)_2$	*t*-BuOMe–THF/−10 °C, 30 min	**2e** (88)[e]	100.0	111.5	2227	nd
6	$-Si(CH_3)_2Ph$	$-Si(CH_3)_2Ph$	*t*-BuOMe–THF/−10 °C, 30 min	**2f** (75)[e]	99.9	111.6	2227	nd
7	$-Si(CH_3)_2-(CH_2)_2-Si(CH_3)_2-$		*t*-BuOMe–THF/−10 °C, 30 min	**2g** (60)[f]	112.4	100.0	2222	322.8
8	$-Si(CH_3)_3$	$-CH_2-Ph$	*t*-BuOMe–THF/−10 °C, 30 min	**2h** (50)[e]	101.5	111.5	nd	nd
9	$-(CH_2)_2-S-(CH_2)_2-$		*t*-BuOMe/−40 °C, 20 min	**2i** (36)[e]	111.3	104.1	2229	294.1
10	$-C(CH_3)_2-CH_2-O-CH_2-C(CH_3)_2-$		*t*-BuOMe/−40 °C, 20 min	**2j** (61)[e]	111.6	101.4	2231	295.5
11	$-(CH_2)_2-NCH_3-(CH_2)_2-$		*t*-BuOMe/−40 °C, 20 min	**2k** (30)[e]	117.1	109.4	2215	nd

nd: not determined.

[a] The metal amide (1 equiv), prepared from the corresponding amine and 1 equiv of *n*-BuLi (commercial solution of LDA and LiHMDS were used), was added to **1** in the indicated solvent at the indicated T °C. Reactions were monitored by TLC (*n*-hexane or *n*-hexane/EtOAc 98:2).

[b] Isolated (unoptimized).

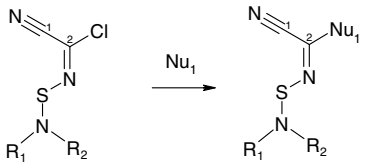
[c] Unstable.

[d] Bp 69–72 °C/0.3 mbar (mp 29–30 °C).

[e] Chromatography.

[f] Bp 72–73 °C/0.3 mbar (mp 38–39 °C).

Table 2. Reaction of 2-chloro-2-[(dialkylaminothio)]imino acetonitriles with nucleophiles



2a-d **3-6**

Entry	Substrate	Nucleophile[a] Nu_1	Experimental conditions[b]	Product	Yield[c] (%)	^{13}C NMR-C^1 (ppm)	^{13}C NMR-C^2 (ppm)	IR-CN (cm^{-1})
1	**2a**	*n*-PrSNa	−20 °C, 1 h	**3a**	20	110.5	122.9	2218
2	**2a**	(4-Me)$PhCH_2SNa$	−20 °C, 1 h	**3b**	25	110.7	122.0	2216
3	**2a**	$PhCH_2OK$	−20 °C, 1 h	**3c**	15	108.2	123.6	2227
4	**2b**	*n*-PrSNa	−20 °C, 1 h	**4a**	91	110.9	121.6	2218
5	**2b**	(4-Me)$PhCH_2SNa$	−20 °C, 1 h	**4b**	84	111.2	120.6	2215
6	**2b**	$PhCH_2OK$	−70 °C, 10 min	**4c**	40	109.6	123.2	2236
7	**2b**	Ph_2CHOK	−70 °C, 10 min	**4d**	70	109.1	121.9	2231
8	**2b**	Me_2NH	20 °C, 2 h	**4e**	95	107.9	125.4	2220
9	**2b**	$PhCH_2NH_2$	20 °C, 2 h	**4f**	90	110.5	123.3	2236
10	**2b**	Morpholine	20 °C, 2 h	**4g**	100	107.9	124.6	2221
11	**2c**	*n*-PrSNa	−40 °C, 15 min	**5a**	50	110.3	126.2	2220
12	**2c**	(4-Me)$PhCH_2SNa$	−40 °C, 15 min	**5b**	60	110.7	125.4	2218
13	**2c**	PhSNa	0 °C, 2 h	**5c**	35	110.4	126.3	nd
14	**2c**	$PhCH_2OK$	−40 °C, 10 min	**5d**	56	108.3	125.5	2226
15	**2c**	Morpholine	20 °C, 1 h	**5e**	30	107.2	127.6	2226
16	**2d**	*n*-PrSNa	−40 °C, 15 min	**6a**	100	111.1	122.7	2216
17	**2d**	(4-Me)$PhCH_2SNa$	−40 °C, 15 min	**6b**	85	111.3	121.6	2215
18	**2d**	$PhCH_2OK$	−40 °C, 15 min	**6c**	85	108.6	123.6	2225
19	**2d**	Piperidine	20 °C, 2 h	**6d**	100	107.9	125.4	2217

[a] All reactions were performed in *t*-BuOMe under nitrogen. Thiolates were prepared from the corresponding thiols and 1 equiv of NaH (*n*-PrSNa is commercially available); alkoxides were prepared from the corresponding alcohols and 1 equiv of *t*-BuOK. The nucleophiles (ca. 1.1 equiv) were added to a solution (ca. 0.5 M) of the substrate.

[b] The reactions were monitored by TLC.

[c] Isolated (chromatography).

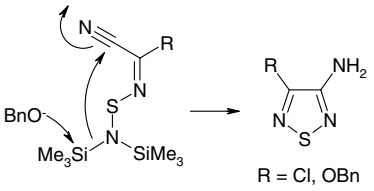
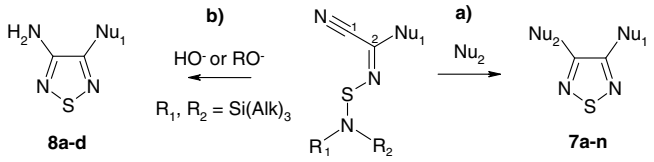


Figure 3.

We performed the ring-closure of compounds **4**–**6** by two different pathways: (a) cyclization induced by O-, N-, S- and C-nucleophiles through an attack on nitrile and (b) cyclization induced by attack on silicon (Table 3). As observed before for substitution, the rate of the ring-closure reaction is highly sensitive to steric hindrance around sulfur (cyclization rate: **5a**–**e** > **4a**–**g** > **6a**–**d**). The cyclization of the 2-substituted-derivatives **4**–**6** with O-, N-, S- or C-nucleophiles afforded the 3,4-disubstituted-1,2,5-thiadiazoles in moderate to high yields. The *N*,*N*-bis-trimethylsilyl compounds **4a**–**f** are particularly attractive as they can be cyclized by both pathways. Indeed, we have shown that the desilylation-induced synthesis of 3-amino-4-substituted-1,2,5-thiadiazoles was particularly effective (entries 18–21). On the other hand, the *N*,*N*-bis-trimethylsilyl derivatives (e.g., **4a**) are also the most appropriate for reactions with carbanions (entries 2–10) including protected amino acids (entries 8–10). For both O- and S-nucleophiles, we carried out the cyclization reactions with a catalytic amount of base as alcohols or thiols are progressively deprotonated by the metal amide released during the reaction. This method allowed us to minimize the side reactions.

In conclusion, we have developed an original approach for the synthesis of 3,4-disubstituted-1,2,5-thiadiazoles from the cheap and readily available 3,4-dichloro-1,2,5-thiadiazole. Although unoptimized, our methodology is already more convenient than most known procedures. The key step is a controlled ring opening reaction with hindered metal amides leading to stable original compounds for the atom connectivity of which was unknown. The reactivity of these intermediates towards nucleophiles is modulated by the bulkiness of the metal amide used in the first step. The most versatile intermediate **2b** is also the most readily obtained. In addition, our methodology offers perspectives for a high throughput solid-phase combinatorial chemistry. Indeed, if a polymer-supported metal amide were used in the first step, the ring-opened product would be grafted to a solid support. After substitution, the unsymmetrical 3,4-disubstituted-1,2,5-thiadiazoles would be released from the solid support by reaction with the second nucleophile.

Table 3. Cyclization of 2-substituted-2-[(dialkylaminothio)]imino acetonitriles with nucleophiles



Entry	Substrate	Nucleophile (Nu_2)/solvent	T (°C)	Product	Yield (%)	Exact mass calcd/found
1	**4a**	HMDS + LiHMDS/THF	65	**7a**	70	319.102848/319.103500
2	**4a**	Phenylacetylene + LDA/THF	−50 to 20	**7b**	73	260.044192/260.043909
3	**4a**	TMS-acetylene + LDA/THF	−25 to 0	**7c**	40	256.052421/256.053273
4	**4a**	*c*-Hex–CO_2Me + LDA/THF	−25	**7d**	88	300.096622/300.096620
5	**4a**	Me_2–CH–CO_2Me + LDA/THF	−25	**7e**	94	260.065322/260.065019
6	**4a**	Me_2N–CH_2–CHMe–CO_2Me + LDA/THF	−25	**7f**	84	303.107521/303.108504
7	**4a**	*N*-Me-ethylpipecolinate + LDA/THF	−25	**7g**	68	329.123171/329.123757
8	**4a**	Me_2N–CH_2–CO_2Et + NaDA/THF	−25	**7h**	86	289.091871/289.091397
9	**4a**	Bn_2N–CH_2–CO_2Et + NaDA/THF	−30 to −10	**7i**	89	nd
10	**4a**	Ph_2C=N–CH_2–CO_2Et + LDA/THF	−30 to 0	**7j**	30	nd
11	**4d**	*n*-PrSH + *n*-PrSNa/THF	20	**7k**	85	342.086057/342.088500
12	**4f**	*n*-PrSH + *n*-PrSNa/THF	20	**7l**	86	265.070741/265.071800
13	**4f**	BnOH + *t*-BuOK/THF	20	**7m**	90	297.093584/294.092400
14	**5a**	BnOH + *t*-BuOK/THF	20	**7n**	80	266.054757/266.053900
15	**5d**	*n*-PrSH + *n*-PrSNa/THF	20	**7n**	50	nd
16	**6c**	*n*-PrSH + *n*-PrSNa/THF	60	**7n**	40	nd
17	**6a**	BnOH + *t*-BuOK/THF	20	**7n**	77	nd
18	**4a**	NaOH/THF–H_2O or K_2CO_3/EtOH	20	**8a**	94	nd
19	**4c**	NaOH/THF–H_2O or K_2CO_3/EtOH	20	**8b**	95	207.046634/207.046800
20	**4d**	NaOH/THF–H_2O or K_2CO_3/EtOH	20	**8c**	62	283.077934/283.078900
21	**4f**	NaOH/THF–H_2O or K_2CO_3/EtOH	20	**8d**	95	206.059246/206.060100

All compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy. Compounds **7i** and **7j** were not analyzed for exact mass (converted to the corresponding amino-acids). Compounds from entries 15–18 were not analyzed for exact mass (entries 15–17 same as entry 14, entry 18 known compd).

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