Synthesis of alkynyl sulfides resulting from a novel ring cleavage of 5-chloro-1,2,3-thiadiazoles in the presence of organometallic reagents

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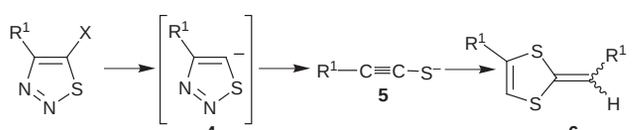
5-Chloro-1,2,3-thiadiazoles **2a**,**b** were treated with organolithium and Grignard reagents giving a novel ring cleavage with the loss of nitrogen and chloride anion, resulting in the formation of alkynyl sulfides **9**–**14**. The results indicate that the mechanism of the reaction involves a concerted *trans*-elimination of the leaving group.

Introduction

The ring cleavage of 4-monosubstituted 1,2,3-thiadiazoles **1** (X = H) in the presence of bases is an effective way of obtaining the reactive alkynethiolates **5**,[1] which can be used in further synthesis, for instance to prepare tetrathiafulvalenes[2] and other dithiole derivatives,[3] or dendrimers.[4] Recently we reported that even weak bases such as phenolate can abstract the proton at the C-5 position of the thiadiazole **1**.[5] This is a disadvantage if we want to introduce the 1,2,3-thiadiazole ring, and hence the alkynethiolate function, into a given molecule by a procedure using this base. Therefore, we were looking for a more robust alternative to the 4-monosubstituted thiadiazole synthon, which we reasoned could be found in the 5-chloro derivative **2** (X = Cl). The thiadiazole ring should remain intact in the presence of weak or moderately strong bases. On the other hand, transmetallation of **2** (X = Cl) with organolithium reagents, is expected to yield the unstable thiadiazolyl anion **4**, which immediately would lose nitrogen to form the alkynethiolate **5**. We can base this assumption on the fact that halogen derivatives of thiophene and thiazole are smoothly lithiated α to the sulfur atom (Scheme 1).

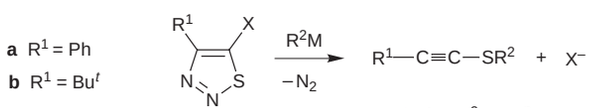


1 R^1 = Ph X = H
2a R^1 = Ph X = Cl
2b R^1 = Bu^t X = Cl
3 R^1 = X = Ph

Scheme 1

Results and discussion

Thus, the 5-chloro-1,2,3-thiadiazoles **2a**,**b** were prepared as previously reported[6] from α-chloromethylene ketones using the Hurd–Mori method.[7] Deprotection of **2a** with butyllithium gave, to our surprise, only a trace amount of the expected dimer **6a** resulting from the alkynethiolate **5a**. On the other hand, the butylsulfanylalkyne **9a** was the major product. In principle, the product **9a** could result from the substitution of chlorobutane with the alkynethiolate **5a**. To disprove this theory, we used phenyllithium, phenylethynyllithium and *tert*-butyllithium as the base in combination with **2a**, and obtained the respective alkyne sulfides **10a**, **11a** and **12a** as the sole isolable products. In these cases, nucleophilic substitution of chlorobenzene, chloroethynylbenzene or *tert*-butyl chloride by alkynethiolate **5a** seems unlikely. In addition, generation of **5a** by an alternative ring cleavage of **1** (X = H, R = Ph) with potassium *tert*-butoxide as base, and subsequent treatment with an excess of chlorobenzene, did not give any sulfide **10a**. To explain the formation of the alkynyl sulfides **9**–**12** we reasoned that the organolithium reagents attack at the sulfur atom of **2**, expelling nitrogen and a chloride ion (Scheme 2). This bears some



2a X = Cl
2b X = Cl
7 X = OPh
8 X = SPh

9a,b R^2 = Bu^n
10a,b R^2 = Ph
11a R^2 = Ph—C≡C
12a R^2 = Bu^t
13a R^2 = Et
14a R^2 = Me

Scheme 2

analogy to the reaction of 4,5-diphenyl-1,2,3-thiadiazole **3** (R = X = Ph) with butyllithium, as investigated by Micetich.[8] Here also, attack occurred on sulfur with cleavage of the N–S bond and subsequent loss of nitrogen, but this time the leaving group was the butylsulfanyl group, resulting in the formation of diphenylacetylene.

Analogously, the 5-chloro-1,2,3-thiadiazole **2b** was treated with butyllithium and phenyllithium to afford respectively the alkynyl sulfides **9b** and **10b**. This procedure constitutes a new and fast entry into alkynyl sulfides, which are interesting compounds that have been used as synthetic intermediates.[9]

Treatment of the 5-chloro-1,2,3-thiadiazole **2a** with Grignard reagents such as phenylmagnesium bromide and ethylmagnesium bromide did not result in conversion at room temperature. However, on heating the reaction mixtures at reflux in THF, the alkynyl sulfides **10a** and **13a** were formed in fair yields.

Nucleophiles such as phenolate and benzenethiolate cleanly substitute **2a** with the formation of the ether **7** or sulfide **8** in excellent yield. It is of interest to observe that the reaction of **7** and **8** with *n*-butyllithium gave **9a** in excellent yield, with the expulsion of the phenolate or benzenethiolate group respectively. The alternative elimination of the butylsulfanyl group, as in the process starting from 4,5-diphenyl-1,2,3-thiadiazole **3**, to form the alkynyl ether, did not take place. This may be an indication that *trans*-elimination of phenolate/benzenethiolate

Table 1 Reaction of 1,2,3-thiadiazoles **2a**,**b**, **7** and **8** with organometallic reagents

R^1	X	R^2	M	Product	Yield (%)
Ph	Cl	Bu	Li	**9a**	63
Ph	Cl	Ph	Li	**10a**	88
Ph	Cl	Ph–C≡C	Li	**11a**	20
Ph	Cl	Bu^t	Li	**12a**	65
Ph	Cl	Et	MgBr	**13a**	61
Ph	Cl	Ph	MgBr	**10a**	55
Bu^t	Cl	Bu	Li	**9b**	56
Bu^t	Cl	Ph	Li	**10b**	67
Ph	OPh	Bu	Li	**9a**	83
Ph	SPh	Bu	Li	**9a**	73

takes place concertedly with the ring cleavage and the loss of nitrogen. *cis*-Elimination probably occurs only when there is no alternative, as for **3**, and may be non-concerted.

Finally, treatment of the 5-chlorothiadiazole **2a** with lithium metal gave, apparently *via* the unstable 1,2,3-thiadiazol-5-yllithium **4**, the alkynethiolate **5a**, which was quenched with methyl iodide to give the expected alkynyl sulfide **14a** in moderate yield. Thus, the 5-chlorothiadiazolyl group is an interesting functionality which can be converted to an alkynyl sulfide in two different ways. The results and yields are summarized in Table 1.

Experimental

IR spectra were recorded on a Perkin Elmer 1720 FT spectrometer and NMR spectra on a Bruker AMX-400 instrument. The NMR spectra were measured in deuteriochloroform solutions with TMS as internal standard; *J* values are given in Hz. Mass spectra (CI) were measured with a Hewlett Packard 5989 A or Kratos MS50 TC (for high resolution) instrument. Melting points were determined using a Reichert Thermovar apparatus.

Compounds **2a** and **2b** were prepared according to the published procedure.[6]

5-Phenoxy-4-phenylthiadiazole 7

A mixture of thiadiazole **2a** (0.507 g, 2.6 mmol), phenol (0.346 g, 3.9 mmol), and K_2CO_3 (0.276 g, 2 mmol) in acetone (10 cm^3) was refluxed for one day. Purification by column chromatography on silica with CH_2Cl_2–hexane (3 : 1) as eluent gave **7** (0.494 g, 75%) as white crystals, mp 103–104 °C (Found: C, 65.8; H, 4.1; S, 12.6. Calc. for $C_{14}H_{10}N_2OS$: C, 65.8; H, 4.1; S, 12.6%); δ_H (400 MHz, $CDCl_3$) 7.28 (2 H, m, *ortho*-H), 7.33 (1 H, m, *para*-H), 7.42–7.53 (5 H, m, *meta*-H, *meta′*-H, *para′*-H), 8.18 (2 H, m, *ortho′*-H); δ_C (100 MHz, $CDCl_3$) 118.6 (d), 126.9 (d), 127.0 (d), 128.6 (d), 128.8 (d), 130.1 (s), 130.6 (d), 146.3 (s), 159.3 (s), 171.8 (s); *m*/*z* (CI) 255 (MH^+, 100%), 227 ($M^+ - N_2$, 13).

5-Phenylsulfanyl-4-phenylthiadiazole 8

A mixture of thiadiazole **2a** (0.484 g, 2.46 mmol), thiophenol (0.33 g, 3 mmol), and K_2CO_3 (0.6 g, 2 mmol) in acetone (10 cm^3) was refluxed for one day. Purification by column chromatography on silica with petroleum ether as eluent gave **8** (0.59 g, 89%) as a red oil, δ_H (400 MHz, $CDCl_3$) 7.39–7.45 (4 H, m, *ortho*-H, *para*-H, *para′*-H), 7.49–7.56 (4 H, m, *meta*-H, *meta′*-H), 7.97 (2 H, m, *ortho′*-H); δ_C (100 MHz, $CDCl_3$) 128.3, 128.7, 128.9, 130.2, 130.7, 132.9, 133.0, 150.5 (s), 156.3 (s); *m*/*z* (CI) 271 (MH^+, 100%), 242 ($M^+ - N_2$, 8) (Found: M^+, 270.0284; $C_{14}H_{10}N_2S_2$ requires: 270.0285).

2-Butylsulfanyl-1-phenylethyne 9a[9a]

A solution of 5-chloro-4-phenylthiadiazole **2a** (0.4 g, 2.04 mmol) in dry THF (10 cm^3) was treated with butyllithium (1 cm^3, 2.5 M solution in hexanes) at −78 °C. The mixture was then stirred at room temperature for one day. After quenching with water (1.5 cm^3) and extraction with CH_2Cl_2 (3 × 10 cm^3), the combined extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica with petroleum ether–diethyl ether (3 : 1) as eluent to give **9a** (0.243 g, 63%) as a yellow oil; ν_{max}/cm^{-1} 2961, 2932, 2168 (C≡C) and 1549; δ_H (400 MHz, $CDCl_3$) 0.98 (3 H, t, *J* 7.3, CH_3), 1.50 (2 H, m, CH_2), 1.80 (2 H, m, CH_2), 2.82 (2 H, t, *J* 7.3, SCH_2), 7.28–7.32 (3 H, m, *meta*-H, *para*-H), 7.43 (2 H, m, *ortho*-H); δ_C (100 MHz, $CDCl_3$) 13.6 (q), 21.5 (t), 31.5 (t), 35.6 (t), 79.7 (s), 92.8 (s), 124.3 (s), 128.6 (d), 129.0 (d), 132.1 (d); *m*/*z* (CI) 191 (MH^+, 100%), 190 (M^+, 14).

A solution of the ether **7** (0.412 g, 1.6 mmol) in THF (10 cm^3) was treated with butyllithium (0.8 cm^3, 2.5 M solution in hexanes) at −78 °C. The mixture was then stirred at room temperature for one day. After quenching with water (1.5 cm^3) and extraction with CH_2Cl_2 (3 × 10 cm^3), the combined extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica with CH_2Cl_2–petroleum ether (3 : 1) as eluent to give **9a** (0.255 g, 83%). Similarly, starting from the sulfide **8**, a 73% yield of **9a** was obtained.

2-Butylsulfanyl-1-*tert*-butylethyne 9b[9a]

Compound **9b** was prepared similarly from 5-chloro-4-*tert*-butylthiadiazole **2b** (0.5 g, 2.83 mmol) and butyllithium (1.5 cm^3, 2.5 M solution in hexanes). Purification by column chromatography on silica with petroleum ether as eluent gave **9b** (0.271 g, 56%) as a colourless oil; ν_{max}/cm^{-1} 2967, 2165 (C≡C), 1722 and 1551; δ_H (400 MHz, $CDCl_3$) 0.93 (3 H, t, *J* 7.3, CH_3), 1.23 (9 H, s, Bu^t), 1.44 (2 H, m, CH_2), 1.70 (2 H, m, CH_2), 2.66 (2 H, t, *J* 7.3, SCH_2); δ_C (100 MHz, $CDCl_3$) 13.5 (q), 21.3 (t), 28.7 (s), 31.0 (q), 31.1 (t), 35.2 (t), 67.1 (s), 102.0 (s); *m*/*z* (CI) 171 (MH^+, 100%), 170 (M^+, 18).

2-Phenylsulfanyl-1-phenylethyne 10a[10]

Compound **10a** was prepared similarly from thiadiazole **2a** (0.486 g, 2.48 mmol) and phenyllithium (2 cm^3, 1.6 M solution in cyclohexane–ether). Purification by column chromatography on silica with petroleum ether–diethyl ether (1 : 1) as eluent gave **10a** (0.458 g, 88%) as a yellow oil; ν_{max}/cm^{-1} 2927, 2173 (C≡C) and 1552; δ_H (400 MHz, $CDCl_3$) 7.24 (1 H, m, *para*-H), 7.33–7.37 (5 H, m, *meta*-H, *meta′*-H, *para*-H), 7.48–7.52 (4 H, m, *ortho*-H, *ortho′*-H); δ_C (100 MHz, $CDCl_3$) 75.5 (s), 97.9 (s), 122.9 (s), 126.2, 126.5, 128.4, 128.6, 129.3, 131.7, 133.0 (s); *m*/*z* (CI) 211 (MH^+, 100%), 210 (M^+, 15).

A mixture of magnesium (0.104 g, 3.46 mmol), bromobenzene (0.507 g, 3.15 mmol) and a catalytic amount of iodine in dry THF (10 cm^3) was transformed into the Grignard reagent. After adding the thiadiazole **2a** (0.389 g, 2 mmol), the mixture was refluxed for one day. After quenching with water (1.5 cm^3) and extraction with CH_2Cl_2 (3 × 10 cm^3), the combined extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica with CH_2Cl_2–hexane (1 : 4) as eluent to give **10a** (0.23 g, 55%) as a yellow oil.

2-Phenylsulfanyl-1-*tert*-butylethyne 10b[11]

Compound **10b** was prepared similarly from thiadiazole **2b** (0.4 g, 2.78 mmol) and phenyllithium (2 cm^3, 1.6 M solution in cyclohexane–ether). Purification by column chromatography on silica with petroleum ether as eluent gave **10b** (0.355 g, 67%) as a colourless oil; ν_{max}/cm^{-1} 2971, 2139 (C≡C), 1716 and 1360; δ_H (400 MHz, $CDCl_3$) 1.31 (9 H, s, Bu^t), 7.16 (1 H, m, *para*-H), 7.29 (2 H, m, *meta*-H), 7.37 (2 H, m, *ortho*-H); δ_C (100 MHz, $CDCl_3$) 29.0 (s), 30.9 (q), 63.4 (s), 107.9 (s), 125.5 (d), 125.9 (d), 129.0 (d), 133.9 (s); *m*/*z* (CI) 191 (MH^+, 79%), 190 (M^+, 14).

Bis(phenylethynyl)sulfane 11a[12]

A solution of phenylethyne (0.265 g, 2.6 mmol) in dry THF (10 cm^3) was treated with butyllithium (0.9 cm^3, 2.5 M solution in hexanes). After ten minutes the thiadiazole **2a** (0.4 g, 2.1 mmol) in dry THF was added. The mixture was stirred at room temperature for one day. After quenching with water (1.5 cm^3) and extraction with CH_2Cl_2 (3 × 10 cm^3), the combined extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica with petroleum ether as eluent to give **11a** (0.096 g, 22%) as a yellow oil; ν_{max}/cm^{-1} 2291 (C≡C), 1549 and 1252; δ_H (400 MHz, $CDCl_3$) 7.32–7.34 (3 H, m, *para*-H, *meta*-H), 7.47 (2 H, m, *ortho*-H); δ_C (100 MHz, $CDCl_3$) 72.0 (s), 94.6 (s), 122.2 (s), 128.4 (d), 129.0 (d), 131.9 (d); *m*/*z* (CI) 234 (M^+, 100%).

2-*tert*-Butylsulfanyl-1-phenylethyne 12a[13]

Compound **12a** was prepared similarly from the thiadiazole **2a** (0.5 g, 2.55 mmol) and *tert*-butyllithium (2 cm^3, 1.5 M solution in pentane). Purification by column chromatography on silica with petroleum ether as eluent gave **12a** (0.313 g, 65%) as a yellow oil; ν_{max}/cm^{-1} 2965, 2165 (C≡C), 1549 and 1366; δ_H (400 MHz, $CDCl_3$) 1.49 (9 H, s, Bu′), 7.29–7.31 (3 H, m, *para*-H, *meta*-H), 7.43 (2 H, m, *ortho*-H); δ_C (100 MHz, $CDCl_3$) 30.5 (q), 48.6 (s), 79.5 (s), 96.7 (s), 124.5 (s), 128.6 (d), 129.0 (d), 132.1 (d); *m*/*z* (CI) 190 (M^+, 8%).

2-Ethylsulfanyl-1-phenylethyne 13a[14]

A solution of thiadiazole **2a** (0.3 g, 1.53 mmol) in dry THF (10 cm^3) was treated with ethylmagnesium bromide (0.9 cm^3, 3.0 M solution in diethyl ether) at −78 °C. The mixture was then refluxed for one day. After quenching with water (1.5 cm^3) and extraction with CH_2Cl_2 (3 × 10 cm^3), the combined extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica with petroleum ether–diethyl ether (4 : 1) as eluent to give **13a** (0.151 g, 61%) as a yellow oil; ν_{max}/cm^{-1} 2967, 2168 (C≡C) and 1550; δ_H (400 MHz, $CDCl_3$) 1.47 (3 H, t, *J* 7.3, CH_3), 2.83 (2 H, q, *J* 7.3, CH_2), 7.29–7.32 (3 H, m, *meta*-H, *para*-H), 7.44 (2 H, m, *ortho*-H); δ_C (100 MHz, $CDCl_3$) 14.7 (q), 29.7 (t), 79.3 (s), 93.5 (s), 123.6 (s), 128.0 (d), 128.3 (d), 131.4 (d); *m*/*z* (CI) 163 (MH^+, 100%), 162 (M^+, 16).

2-Methylsulfanyl-1-phenylethyne 14a[14]

A mixture of thiadiazole **2a** (0.454 g, 2.3 mmol) and lithium (0.055 g, 7.9 mmol) in dry THF (10 cm^3) was stirred at room temperature for five hours. Then, iodomethane (1.5 g, 10.5 mmol) was added and the mixture was further stirred overnight. After quenching with water (1.5 cm^3) and extraction with CH_2Cl_2 (3 × 10 cm^3), the combined extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica with petroleum ether as eluent to give **14a** (0.144 g, 34%) as a yellow oil; ν_{max}/cm^{-1} 2929, 2169 (C≡C), 1551 and 1252; δ_H (400 MHz, $CDCl_3$) 2.46 (3 H, s, CH_3), 7.26–7.28 (3 H, m, *meta*-H, *para*-H), 7.40 (2 H, m, *ortho*-H); δ_C (100 MHz, $CDCl_3$) 19.3 (q), 80.9 (s), 91.8 (s), 123.4 (s), 128.0 (d), 128.2 (s), 131.4 (d); *m*/*z* (CI) 149 (MH^+, 80%), 148 (M^+, 11).

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References

1 R. Raap, *Can. J. Chem.*, 1968, **46**, 2251.
2 R. Andreu, J. Garin, J. Orduna, M. Saviron, J. Cousseau, A. Gorgues, V. Morisson, T. Nozdryn, J. Becher, R. P. Clausen, M. R. Bryce, P. J. Skabara and W. Dehaen, *Tetrahedron Lett.*, 1994, **35**, 9243.
3 A. Shafiee and I. Lalezari, *J. Heterocycl. Chem.*, 1973, **10**, 11.
4 G. L'abbé, B. Haelterman and W. Dehaen, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 2203.
5 B. D'hooge, S. Smeets and W. Dehaen, *Chem. Commun.*, 1997, 1753.
6 E. Schaumann, J. Ehlers and H. Mrotzek, *Liebigs Ann. Chem.*, 1979, 1734.
7 C. D. Hurd and R. I. Mori, *J. Am. Chem. Soc.*, 1955, **77**, 5359.
8 R. G. Micetich, *Org. Prep. Proced. Int.*, 1971, 163.
9 (*a*) M. Hoshi, Y. Masuda and A. Arase, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 447; (*b*) P. A. Magriotis, J. T. Brown and M. E. Scott, *Tetrahedron Lett.*, 1991, **32**, 5047; (*c*) J. J. Eisch, H. Gopal and S. Rhee, *J. Org. Chem.*, 1975, **40**, 2064.
10 W. E. Truce, H. E. Hill and M. M. Boudakian, *J. Am. Chem. Soc.*, 1956, **78**, 2760.
11 R. S. Glass and Q. Guo, *Tetrahedron*, 1997, **53**, 12273.
12 (*a*) W. Verboom, M. Schoufs, J. Meijer, H. D. Verkruijsse and L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, 1978, **97**, 244; (*b*) M. Herres, O. Walter, H. Lang, R. Hosch and J. Hahn, *J. Organomet. Chem.*, 1994, **466**, 237.
13 A. L. Braga, O. E. D. Rodrigues, E. de Avila and C. C. Silveira, *Tetrahedron Lett.*, 1998, **39**, 3395.
14 R. Raap and R. G. Micetich, *Can. J. Chem.*, 1968, **46**, 1057.

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