Reactions of Lithiated 1,2,3-Thiadiazoles: Synthesis of 4-Substituted 1,2,3-Thiadiazoles

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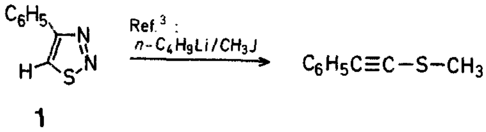
Metalation of 5-phenyl-1,2,3-thiadiazole (**2**) with methyllithium affords 4-lithio-5-phenyl-1,2,3-thiadiazole, which is stable and reacts with aldehydes and ketones to give 4-substituted 1,2,3-thiadiazoles **3** in excellent yields. Treatment of 4-phenyl-1,2,3-thiadiazole (**1**) with lithium diisopropylamide, in the presence of chlorotrimethylsilane, affords 4-phenyl-5-trimethylsilyl-1,2,3-thiadiazole (**7**).

The chemistry and the synthetic applications of metalated heterocycles such as furans, thiophenes, thiazoles, and isoxazoles have been well documented[1]. Although the literature in this area is extensive, there are few references to the metalation of 1,2,3-thiadiazoles. The paucity of references may reflect the fact that researchers have focused mainly on the thermal and photochemical reactions of 1,2,3-thiadiazoles, which afford acetylenes and thiirenes[2].

Raap and Micetich[3] were the first to explore the rich chemistry of metalated 1,2,3-thiadiazoles and they found that under the metalation conditions 4-phenyl-1,2,3-thiadiazole (**1**) and 5-phenyl-1,2,3-thiadiazole (**2**) react differently. *n*-Butyllithium deprotonated 4-phenyl-1,2,3-thiadiazole (**1**) affording the corresponding anion which extruded nitrogen and produced lithium 2-phenylethynethiolate. This was alkylated with numerous alkyl halides in good yield (Scheme A). Methyllithium metalated 5-phenyl-1,2,3-thiadiazole (**2**) at −65 °C and the thiadiazole anion was alkylated with methyl iodide to give the 4-methyl derivative **3**. Attempts at metalation with *n*-butyllithium resulted in only trace amounts of product. We believe this example is the only report, to date, of the alkylation of a metalated 1,2,3-thiadiazole.



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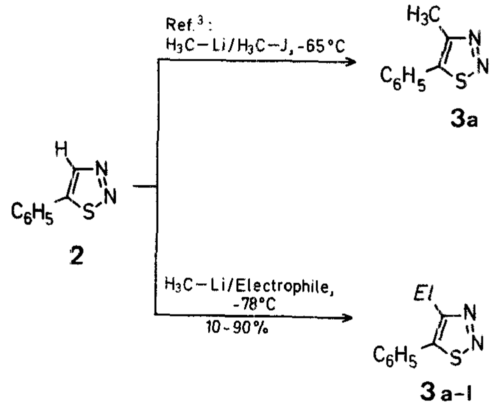
Scheme **A**

We were quite intrigued by these observations which stimulated us to answer the following questions:

- since 4-lithio-5-phenyl-1,2,3-thiadiazole has only been alkylated with methyl iodide, is this reaction general for a variety of electrophiles?
- secondly, is it possible to metalate 4-phenyl-1,2,3-thiadiazole (**1**) and then alkylate the 5-lithio species at low temperature before it decomposes?

Following the procedure of Raap and Micetich[3] we metalated 5-phenyl-1,2,3-thiadiazole (**2**) in tetrahydrofuran with methyllithium at −78 °C and quenched the anion with methyl iodide affording **3a** in 64% yield (Scheme **B**). Under similar conditions we alkylated 4-lithio-5-phenyl-1,2,3-thiadiazole with benzyl bromide to afford **3b** in 12% yield, yet with *n*-butyl bromide and *n*-butyl iodide we obtained no product. In order to increase the yield of reaction, e.g. with *n*-butyl iodide, the reaction temperature was raised. However, 4-lithio-5-phenyl-1,2,3-thiadiazole decomposed above −40 °C to nearly 25 compounds as determined by T.L.C. The major reaction product was elemental sulfur (30%) and the only other product isolated was (*E*)-2,3-diphenyl-2-butenedinitrile (5%)[4].

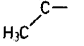
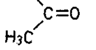
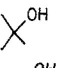
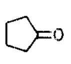
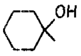
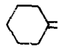
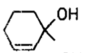
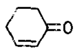
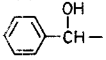
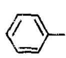
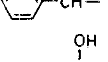
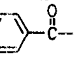
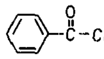
Aldehydes and ketones proved much more reactive than alkyl halides with 4-lithio-5-phenyl-1,2,3-thiadiazole. In these reactions, 4-lithio-5-phenyl-1,2,3-thiadiazole was generated as before at −78 °C with methyllithium. The anion reacted with various ketones and aldehydes at −78 °C (Scheme **B**). Simple aqueous workup and chromatography afforded the alcohols **3c–j** in high yields (Table).



3a

2

3a-l

3	*El*	Electrophile
a	H_3C	H_3C-J
b		
c		
d		
e		
f		
g		
h	$n\text{-}C_3H_7-\overset{OH}{\overset{\vert}{C}}H-$	$n-C_3H_7-\overset{OH}{\overset{\vert}{C}}H{=}O$
i	$C_2H_5-\overset{OH}{\overset{\vert}{C}}H-$	$C_2H_5-CH{=}O$
j	$n-C_7H_{15}-\overset{OH}{\overset{\vert}{C}}H-$	$n-C_7H_{15}-CH{=}O$
k		
l	HOOC	CO_2

Scheme **B**

A few additional electrophiles were reacted with 4-lithio-5-phenyl-1,2,3-thiadiazoles. Carbon dioxide affords **3l** in moderate yield while benzoyl chloride afforded ketone **3k** in poor yield (Table). These examples demonstrate that this is a facile method for introduction of a variety of substituents at the 4-position of 5-phenyl-1,2,3-thiadiazoles (**2**).

We have explored the possibility of generating 5-lithio-4-phenyl-1,2,3-thiadiazole (**4**) at low temperature and trapping the anion, before it could decompose, with an electrophile. Raap[5] has shown that treatment of 4-phenyl-1,2,3-thiadiazole (**1**) at −60 °C with methyllithium followed by a water quench affords 5-phenyl-2-(phenylmethylene)-1,3-dithiole (**6**), a yellow solid, presumably via the thioketene **5** (Scheme **C**). We metalated **1** at −78 °C with methyllithium and upon addition of water we also obtained **6**. Since we have earlier[6] synthesized 4-deutero-5-phenyl-1,2,3-thiadiazole by

Table. Alkylation of 4-Lithio-5-phenyl-1,2,3-thiadiazole, obtained from **2** and Methyllithium with Electrophiles

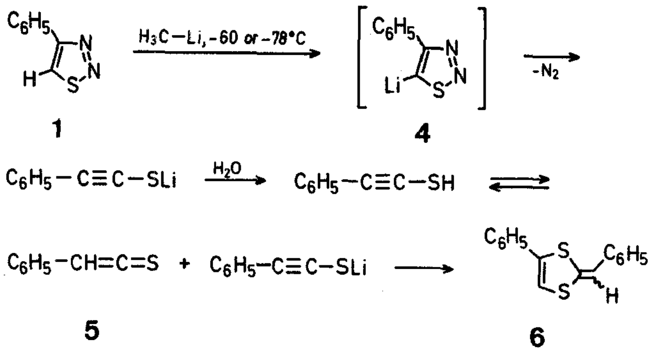
Product	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[a] or Lit. data	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ [ppm]	^{13}C-N.M.R. (CDCl$_3$/TMS) ϱ [ppm]	M.S. (70 eV) *m/e* (M$^+$)
3a	64		b.p. 82–83°/0.1	2985, 1445, 1240, 810, 695	2.78 (s, 3H, CH_3); 7.52 (s, 5H_{arom})		176
3b	12	100°/0.05	$C_{15}H_{12}N_2S$ (252.3)	3062, 1495, 1227, 831, 718	4.36 (s, 2H, CH_2); 7.17 (s, 5H, CH_2—$C_6\underline{H}_5$); 7.40 (s, 5H_{arom})	157.5 (C—N), 151.7 (C—S), 138.57, 129.7, 129.3, 129.1, 128.6, 127.9, 127.4, 126.6, 32.9	252
3c	76	87–89°	$C_{11}H_{12}N_2OS$ (220.3)	3400, 1580, 1510, 1220, 1160, 1125, 975, 865, 760, 695	1.63 (s, 6H, CH_3); 3.40 (s, 1H, OH); 7.46 (s, 5H_{arom})	164.8 (C—N), 151.1 (C—S), 130.1, 129.5, 128.5, 127.9, 72.0, 31.3	220
3d	83	97–98°	$C_{13}H_{14}N_2OS$ (246.3)	3560, 2950, 1440, 1220, 1000, 695	1.58–2.32 (m, 8H, CH_2); 2.86 (br. s, 1H, OH); 7.50 (s, 5H_{arom})	165.4 (C—N), 152.3 (C—S), 130.1, 129.6, 128.5, 128.1, 81.2, 41.3, 23.6	246
3e	80	70.5–72°	$C_{14}H_{16}N_2OS$ (260.4)	3570, 2940, 1440, 1260, 980, 690	1.32–2.15 (m, 10H, CH_2); 2.53 (br. s, 1H, OH); 7.45 (s, 5H_{arom})	164.6 (C—N), 151.7 (C—S), 130.0, 129.4, 128.4, 128.3, 39.0, 25.3, 21.0	260
3f	62	84–86°	$C_{14}H_{14}N_2OS$ (258.3)	3540, 2940, 1440, 1235, 990, 890, 695	1.58–2.41 (m, 6H, CH_2); 3.32 (s, 1H, OH); 5.83 (br. s, 2H_{olefin}); 7.46 (s, 5H_{arom})	163.5 (C—N), 152.2 (C—S), 130.9, 130.6, 130.2, 129.5, 128.4, 127.8, 70.7, 37.8, 24.8, 13.7	258
3g	90	172–174°	$C_{15}H_{12}N_2OS$ (268.3)	3333, 2926, 1453, 745, 697	3.51 (br. s, 1H, C$\underline{H}$—OH); 6.10 (br. s, 1H, OH); 7.38 (m, 10H_{arom})	159.9 (C—N), 152.7 (C—S), 141.9, 130.0, 129.6, 129.1, 128.5, 127.9, 126.8, 69.5	268
3h	85		$C_{12}H_{14}N_2OS$ (234.3)	3400, 2960, 1440, 1270, 820, 695	0.83 (t, 3H, J = 7 Hz, CH_3); 1.10–1.60 (m, 2H, C$\underline{H}_2$—CH_3); 1.90–2.30 (m, 2H, CH_2—C—O), 3.27 (d, 1H, J = 7 Hz, OH); 4.92 (m, 1H, C$\underline{H}$—O); 7.41 (s, 5H_{arom})	159.9 (C—N), 152.7 (C—S), 141.9, 130.0; 129.3, 127.5, 67.2, 40.0, 19.1, 13.8	234
3i	72		$C_{11}H_{12}N_2OS$ (220.3)	3405, 2965, 1444, 1248, 828, 695	0.90 (t, 3H, J = 7 Hz, CH_3); 2.11 (quintet, 2H, J = 7 Hz, CH_2); 3.21 (br. s, 1H, OH); 4.89 (t, 1H, J = 7 Hz, CH—O); 7.50 (s, 5H_{arom})	160.6 (C—N), 152.8 (C—S), 130.0, 129.6, 129.3, 127.5, 68.9, 30.9, 10.3	220
3j	83		$C_{16}H_{21}N_2OS$ (289.4)	3420, 1445, 1260, 830, 705	0.75–1.00 (m, 3H, CH_3); 1.01–1.50 (m, 10H, CH_2); 1.90–2.35 (m, 2H, CH_2—C—O); 3.43 (br. s, 1H, OH); 4.80–5.20 (m, 1H, CH—O); 7.50 (s, 5H_{arom})	160.8 (C—N), 152.2 (C—S), 130.0, 129.3, 127.5, 67.5, 37.9, 31.8, 29.3, 29.2, 25.8, 22.6, 14.1	290
3k	10	86.5–87°	$C_{15}H_{10}N_2OS$ (266.3)	2925, 1657, 1597, 1465, 1329	7.28–7.75 (m, 8H_{arom}); 7.95–8.23 (m, 2H_{arom})	187.5, 160.6 (C—N), 155.0 (C—S), 137.0, 133.8, 130.7, 129.7, 129.1, 128.9, 126.4	266
3l	45	140–145°	$C_9H_6N_2O_2S$ (206.2)	2710, 2600, 1690, 1460, 1370	7.60 (m, H_{arom})	161.4, 160.4, 149.5, 130.4, 129.7, 128.6, 126.1[b]	206

[a] Satisfactory microanalyses obtained: C ± 0.38, H ± 0.24, N ± 0.38, S ± 0.38 (Exception, 3h, S + 0.41).

[b] In dimethyl sulfoxide solution.

metalating 5-phenyl-1,2,3-thiadiazole (**2**) with methyllithium followed by quenching with 38 % deuterium chloride in deuterium oxide, we attempted to synthesize 5-deutero-4-phenyl-1,2,3-thiadiazole in the same manner. At − 100 °C, 4-phenyl-1,2,3-thiadiazole (**1**) was metalated with methyllithium and upon quenching with 38 % deuterium chloride in deuterium oxide the reaction turned dark yellow, an indication the 1,3-dithiole had been formed, which was confirmed by comparison to authentic **6** by T.L.C. We were prohibited from exploring the reaction at lower temperatures because below − 100 °C the solution froze.

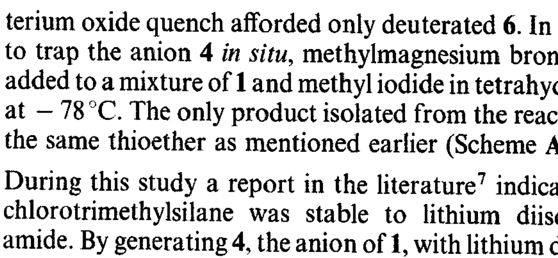
A more covalent metal to carbon bond, than lithium to carbon in tetrahydrofuran, intuitively should retard the thermal decomposition of this heterocyclic system. However, metalation of **1** with methylmagnesium bromide followed by deu-



Scheme C

terium oxide quench afforded only deuterated **6**. In an effort to trap the anion **4** *in situ*, methylmagnesium bromide was added to a mixture of **1** and methyl iodide in tetrahydrofuran at − 78 °C. The only product isolated from the reaction was the same thioether as mentioned earlier (Scheme **A**).

During this study a report in the literature[7] indicated that chlorotrimethylsilane was stable to lithium diisopropylamide. By generating **4**, the anion of **1**, with lithium diisopropylamide we were able to trap the anion **4** *in situ* with chlorotrimethylsilane, before fragmentation occurred, to give **7** (Scheme **D**).



Scheme D

In summary, alkylation of 4-lithio-5-phenyl-1,2,3-thiadiazole (**4**) proceeds readily with aldehydes and ketones. The reaction with alkyl halides is not general as the anion decomposes above − 40 °C. Further, 4-phenyl-1,2,3-thiadiazole (**1**) can be metalated and trapped with an electrophile before decomposition occurs.

I.R. spectra were recorded on a Perkin Elmer 297 spectrometer. ^{1}H-N.M.R. spectra were recorded on a Varian EM-390 (90 MHz) spectrometer. ^{13}C-N.M.R. were recorded on a Varian CFT-20 spectrometer. Melting points were taken on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Mass spectra were recorded on a Varian MAT-CH5 spectrometer. Unless specified all solvents and reagents were used without further purification. Tetrahydrofuran was dried over 4 Å molecular sieves[8]. All reactions were conducted in an atmosphere of nitrogen.

1-(5-Phenyl-1,2,3-thiadiazole-4-yl)-1-cyclohexanol (3e); Typical Procedure:

5-Phenyl-1,2,3-thiadiazole (**2**; 5.0 g, 30.9 mmol) is dissolved in tetrahydrofuran (75 ml) and cooled to − 70 °C. Methyllithium (25.0 ml, 31 mmol, 1 molar in ether) is slowly added to the reaction. After 15 min cyclohexanone (3.02 g, 30.9 mmol) dissolved in tetrahydrofuran (10 ml) is added to the dark brown mixture. The reaction is kept at − 78 °C for an additional 20 min and then kept at room temperature for 1 h. The reaction is quenched by the cautious addition of water (40 ml). The aqueous portion is extracted twice with ether (2 × 70 ml) and the organic portions are combined, dried over magnesium sulfate, and the solvent is removed *in vacuo*. The crude solid is recrystallized from ether and the mother liquors were chromatographed on silica gel eluting with dichloromethane; total yield: 6.43 g (80 %); m.p. 70.5–72.0 °C.

The products **3a–d**, **3f–k** are prepared in the same way and purified as given below.

3a: Upon workup the compound is purified by column chromatography on silica gel using dichloromethane as eluent.

3b: The purification is effected by column chromatography on silica gel using dichloromethane/hexane (1 : 1) as eluent.

3c: Recrystallization from hexane yielded pure product.

3d: Pure product is obtained by recrystallization from ether and further quantities are obtained from the mother liquor by chromatography on silica gel using dichloromethane as eluent.

3f: The compound is purified by chromatography on silica gel using dichloromethane as eluent followed by recrystallization from ether.

3g: The crude brown solid is recrystallized from ether and further quantities are obtained by chromatography on silica gel using dichloromethane as eluent.

3h, i: The crude oily products are chromatographed on silica gel using hexane/ethyl acetate (3 : 1) as eluent.

3j: Column chromatography on silica gel using hexane/ethyl acetate (4 : 1) affords the pure product.

3k: The compound is chromatographed on silica gel using dichloromethane/hexane (65 : 35) as eluent.

5-Phenyl-1,2,3-thiadiazole-4-carboxylic acid (3l):

5-Phenyl-1,2,3-thiadiazole (**2**; 4.0 g, 24.7 mmol) is dissolved in tetrahydrofuran (40 ml) and cooled to − 78 °C. Methyllithium (16 ml, 24 mmol, 1.5 molar in ether) is added to the reaction and it turns deep red. After 5 min carbon dioxide is bubbled through the reaction for 45 min at − 78 °C. Then the reaction is poured over solid carbon dioxide. A saturated solution of aqueous sodium hydrogen carbonate (25 ml) is added and the mixture is extraced with ether (2 × 25 ml). The aqueous portion is acidified to pH 2 with 10 % aqueous hydrochloric acid. The precipitate is filtered and dried in a vacuum oven overnight affording **3l**; yield: 3.15 g (62 %); m.p. 140–145 °C (decom.). This material is purified by recrystallization from ether; yield: 2.3 g (45 %). The mother liquor is chromatographed on silica gel using dichloromethane/acetic acid (5 %) to afford a further quantity (130 mg, 3 %) of **3l**.

4-Phenyl-5-trimethylsilyl-1,2,3-thiadiazole (7):

Thiadiazole **1** (10.0 g, 61.7 mmol) dissolved in tetrahydrofuran (250 ml, dried over molecular sieves) is cooled to − 78 °C and chlorotrimethylsilane (7.83 ml, 61.7 mmol, distilled from calcium hydride) is added. Lithium diisopropylamide [generated from diisopropylamine (6.2 g, 62 mmol), in tetrahydrofuran (40 ml) and *n*-butyllithium (41.3 ml, 62 mmol, 1.5 molar in hexane) first at − 78 °C and then at 0 °C for 40 min] is cooled to − 60 °C and is added via a cannula to the reaction. After 2 min T.L.C. analysis reveals the reaction was complete. The reaction is warmed to room temperature and evaporated in *vacuo*. The residue is triturated with hexane (250 ml) and heated on a steam bath and then filtered to remove lithium chloride. The filtrate is concentrated and chromatographed on silica gel (100 g) using hexane/ethyl acetate (9 : 1) to yield a pure fraction which is recrystallized from hexane to give **7**; yield: 5.24 g (36 %); m.p. 92–94 °C. The less pure material is rechromatographed and recrystallized from hexane to give a further quantity of **7** (2.34 g); m.p. 92–94 °C. By the same procedure 400 mg of **7** is recovered from the mother liquors; total yield: 7.98 g (55 %).

$C_{11}H_{14}N_2SSi$	calc.	C 56.37	H 6.02	N 11.95	S 13.68
(234.4)	found	56.16	6.14	11.88	13.26

I.R. (Nujol): ν = 2995, 2928, 1451, 1431, 1253, 1014, 913, 855, 845 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/acetone): $\delta = 0.15$ [s, 9H, Si(CH$_3$)$_3$]; 2.00 (acetone, internal standard); 7.30–7.68 ppm (m, 5H$_{arom}$).

M.S.: $m/e = 234$ (M$^+$).

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