Preparation of β-Hydroxysulfides from 1,2,3-Thiadiazoles. Comparison of the Effect of Phenylmagnesium Bromide on α-Thio- and α-Selenoketones

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Base decomposition of 4-substituted-phenyl-1,2,3-thiadiazoles at 78° resulted in 2-(4-substituted-phenyl)-ethynylthiolate anions which were immediately reacted with α-bromoketones to give a series of α-(2-[4-substituted-phenyl]ethynyl) thioketones. Unlike the selenophilic reaction of the Grignard reagents with α-selenoketones, the carbonyl group was the site of nucleophilic attack and the reaction of the α-thioketones with phenylmagnesium bromide gave the corresponding β-hydroxysulfides. The difference in mode of action toward the Grignard reagents was attributed to the difference in the bond strengths between carbon and the heteroatoms.

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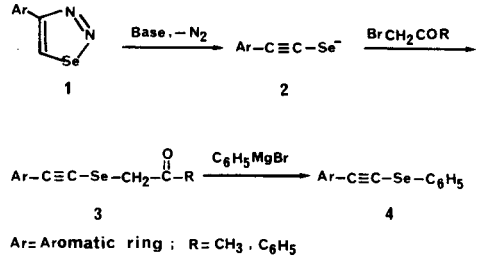
In continuation of our interest in the chemistry of 1,2,3-selenadiazoles **1** [1-3], in a previous investigation [4] we prepared α-selenoketones **3** from 4-aryl-1,2,3-selenadiazoles and examined the action of phenylmagnesium bromide on the α-selenoketones **3**. We concluded that selenium, instead of the competitive carbonyl group, was the site of nucleophilic attack by the organic group of the Grignard reagent. This selenophilic reaction represents a route to the preparation of selenoethers **4** (Scheme 1).

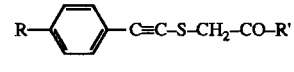
Scheme 1



In view of the interesting aspect of this selenophilic reaction we decided to extend the scope of the reaction to the corresponding α-thioketones **8** (Scheme 2). In the present work, the synthesis of α-thioketones **8** from 4-aryl-1,2,3-thiadiazoles **5** is described and the action of phenylmagnesium bromide **9** on α-thioketones is studied. 1,2,3-Thiadiazoles **5** [5 and 6] were prepared from the reaction of the corresponding arylketone semicarbazones with thionyl chloride. The 2-arylethynylthiolate anions **6**

Table I

α-(2-[4-Substituted-phenyl]ethynyl)thioketones **8**

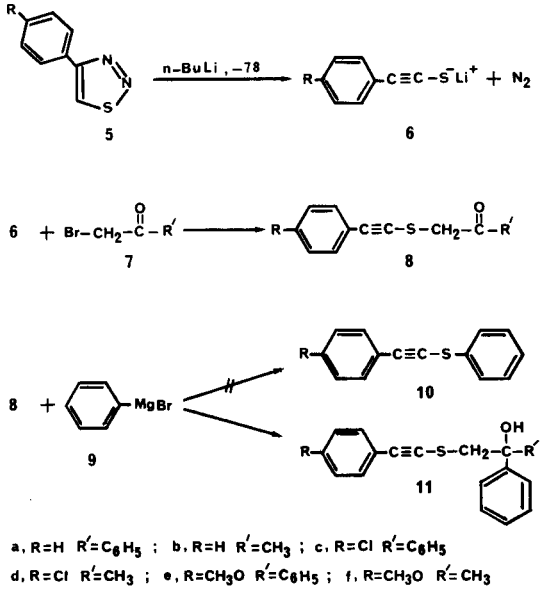


No.	R	R'	Mp°C	Yield %	Formula	Analysis Calcd. C%	Analysis (Found) H%	IR, C≡C	IR, cm⁻¹ C=O	¹H-NMR, ppm
8a	H	C_6H_5	oil [a]	70	$C_{16}H_{12}OS$	76.16 (76.38)	4.79 (4.76)	2190	1690	4.2 (s, 2H), 6.8-7.9 (m, 10H)
8b	H	CH_3	oil [a]	30	$C_{11}H_{10}OS$	69.44 (69.37)	5.30 (5.34)	2180	1720	2.3 (s, 3H), 3.5 (s, 2H), 7.0-7.5 (m, 5H)
8c	Cl	C_6H_5	74-75 [b]	94	$C_{16}H_{11}ClOS$	67.01 (66.95)	3.87 (3.87)	–	1670	4.3 (s, 2H), 7.3-8.1 (m, 9H)
8d	Cl	CH_3	33-34 [a,c]	55	$C_{11}H_9ClOS$	58..80 (58.79)	4.04 (4.05)	2190	1700	2.4 (s, 3H), 3.6 (s, 2H), 7.3 (s, 4H)
8e	CH_3O	C_6H_5	79-80 [b]	95	$C_{17}H_{14}O_2S$	72.31 (72.20)	4.99 (5.01)	2190	1690	3.7 (s, 3H), 4.2 (s, 2H), 6.7-8.1 (m, 9H)
8f	CH_3O	CH_3	45 [a,c]	91	$C_{12}H_{12}O_2S$	65.43 (65.59)	5.49 (5.50)	2200	1720	2.4 (s, 3H), 3.5 (s, 2H), 3.8 (s, 3H), 6.7 (d, 2H), 7.5 (d, 2H)

[a] Purified by column flash chromatography using ethyl acetate-hexane as the eluent. [b] Rectrystallized from methanol. [c] Yellow oil which solidified after three weeks, in the refrigerator.

were generated *in situ* by the addition of *n*-butyllithium or methyllithium, at −78° to a solution of 1,2,3-thiadiazoles **5** in tetrahydrofuran. Immediately after the evolution of nitrogen gas the corresponding α-haloketones **7** were added. Decomposition of the thiadiazoles to thiolate anions by potassium *t*-butoxide at 0° [6] was not successful and the starting materials were recovered. The structure of all α-thioketones **8** were confirmed by analytical and spectroscopic methods. The results are tabulated in Table I.

Scheme 2



To study the behavior of these α-thioketones **8** toward Grignard reagents they were reacted with phenylmagnesium bromide (**9**) in tetrahydrofuran. In contrast to the selenium analogs [4] the carbonyl group was the site of nucleophilic attack by the Grignard reagent. In all cases, after the reaction work up and purification by column flash chromatography the corresponding β-hydroxysulfides **11** were separated, Table II.

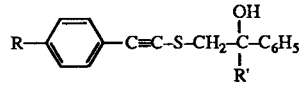
The difference in reactivity between α-selenoketones **3** and α-thioketones **8** toward the Grignard reagents could be attributed to the difference in the carbon-heteroatom bond strengths. Considering that the chemistry of the elements, sulfur and selenium, is qualitatively similar, some features of selenium compounds make them more suitable for synthetic transformations. However, since carbon-sulfur bonds are much stronger than carbon-selenium bonds [8] the sulfur analogs, in this case, resist the thiophilic reaction which involves the cleavage of a carbon-sulfur bond and formation of the corresponding thioethers **10**. Instead, the nucleophilic attack by the organic group of the Grignard reagent occurs on a more favorable site which is the carbon of the carbonyl group, leading to the formation of β-hydroxysulfides **11**.

EXPERIMENTAL

Melting points were determined with Fisher-Johns hot stage apparatus. The nmr spectra were recorded on a Varian LM-360 instrument. Chemical shifts are reported on δ scale relative to tetramethylsilane in deuteriochloroform. Infrared spectra were obtained from a Perkin Elmer Infracord spectrophotometer. The

Table II

(2-[4-Substituted-phenyl]ethynyl)-1-phenyl-1-methyl(or phenyl)ethan-1-ol Sulfides **11**



No.	R	R'	Yield [a] %	Formula	Analysis Calcd. C%	Analysis (Found) H%	IR, C≡C	IR, cm^{-1} OH	^{1}H-NMR, ppm
11a	H	C_6H_5	50	$C_{22}H_{18}OS$	79.96 (79.88)	5.49 (5.50)	2200	3500	3.2 (s, OH), 3.7 (s, 2H), 7-7.5 (m, 15H)
11b	H	CH_3	45	$C_{17}H_{16}OS$	76.08 (76.15)	6.01 (6.00)	2200	3500	1.7 (s, 3H), 2.9 (s, OH), 3.3 (s, 2H), 7.0-7.5 (m, 10H)
11c	Cl	C_6H_5	62	$C_{22}H_{17}ClOS$	72.42 (72.56)	4.70 (4.65)	2180	3500	3.2 (s, OH), 3.7 (s, 2H), 7.1-7.6 (m, 14H)
11d	Cl	CH_3	75	$C_{17}H_{15}ClOS$	67.43 (67.35)	4.99 (4.96)	2180	3500	1.7 (s, 3H), 2.7 (s, OH), 3.4 (s, 2H), 7.3-7.6 (m, 9H)
11e	CH_3O	C_6H_5	56	$C_{23}H_{20}O_2S$	76.64 (76.56)	5.59 (5.70) [b]	2200	3600	3.2 (s, OH), 3.6 (s, 5H), 6.6-7.5 (m, 14H)
11f	CH_3O	CH_3	52	$C_{18}H_{18}O_2S$	72.45 (72.29)	6.08 (5.95)	2200	3600	1.7 (s, 3H), 2.8 (s, OH), 3,3 (s, 2H), 3.8 (s, 3H), 6.7-7.5 (m, 9H)

[a] They were all oils and purified by flash column chromatography using chloroform-hexane as the eluent. [b] Sulfur analysis Calcd. 8.89; Found 8.85.

compounds were used as a thin film or Nujol mull. Silica gel for flash column chromatography with an average particle size of about 40 μm were obtained from J. T. Baker Chemical Co. The starting 4-substituted 1,2,3-thiadiazoles **5** were prepared similar to previously described methods [5,7].

α-Thioketones **8a-f**.

General Procedure.

A 1.6 *M* solution of *n*-butyllithium in *n*-hexane (6.8 ml, 0.011 mole of butyllithium) was added dropwise to a stirred solution of 4-substituted 1,2,3-thiadiazole **5** (0.01 mole) in anhydrous tetrahydrofuran (35 ml) kept at −78° in a dry ice-acetone bath. The addition was carried out in a nitrogen atmosphere and at such a rate (45 minutes) that the temperature of the mixture did not exceed −65°. When the addition was complete it was stirred at −65° for an additional 10 minutes. To the reddish reaction mixture the appropriate α-bromoketone **7** (0.01 mole) was added in one portion. The solution was allowed to warm to 0° and added to a mixture of ice and water (200 ml). The mixture was extracted with ether (3 x 100 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed under reduced pressure and the solid was recrystallized from ethanol or methanol. For the preparation of compounds **8a,d,f**, 1.4 *M* methyllithium, instead of 1.6 *M* *n*-butyllithium, was used. For physical and spectroscopic data see Table I.

β-Hydroxysulfides **11a-f**.

General Procedure.

A solution of α-thioketone **8** (0.003 mole) in anhydrous tetrahydrofuran (20 ml) was added to a 3.0 *M* diethyl ether solution of phenylmagnesium bromide (1.25 ml, 0.0037 mole) in tetrahydrofuran (20 ml) in 10 minutes, at room temperature and under dry nitrogen gas. The mixture was refluxed for two hours. After cooling to room temperature, it was hydrolyzed by pouring the content over 10% sulfuric acid (15 ml) and crushed ice, and was extracted with ether (3 x 60 ml). The ether solution was washed with saturated sodium bicarbonate and after drying on magnesium sulfate the solvent was evaporated under reduced pressure. The oily residue was subjected to flash column chromatography using chloroform-hexane as eluent and in different proportions, based on the nature of the product, to give $R_f = 0.3$ on silica gel tlc for the least polar component of the mixture. The use of ethyl acetate-hexane as the tlc eluent resulted in only one spot which was misleading. For physical and spectroscopic data see Table II.

REFERENCES AND NOTES

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