Reaction of Diethyl Carbonate with 4-Substituted Thiosemicarbazides

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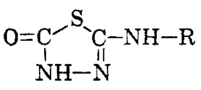
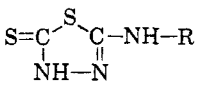
In connection with our studies in the 1,3,4-thiadiazole series[1] we were interested in the preparation of some substituted 2-amino-Δ^2-1,3,4-thiadiazoline-5-ones (I., or tautomeric forms). First we attempted to prepare these compounds from the corresponding sulfur analogs (II) by desulfurization, but a variety of reagents was not effective in bringing about this conversion.



I



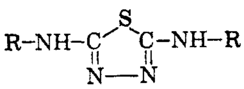
II

Of particular interest was the hitherto unknown reaction between diethyl carbonate and 4-substituted thiosemicarbazides which might lead to the desired products in a direct reaction sequence. The reaction, however, took a quite different course. When refluxing 4-phenylthiosemicarbazide and diethyl carbonate in ethylene glycol monomethyl ether, 2,5-dianilino-1,3,4-thiadiazole (III, R = C_6H_5—)[2] was obtained, but performing the same experiment in the presence of some hydrochloric acid, it was possible to isolate 1,6-diphenylbithiourea as an intermediate product. The last mentioned compound was obtained also when 4-phenylthiosemicarbazide was treated with ethyl chloroformate in the presence of sodium ethoxide while on the other hand the presence of anhydrous sodium acetate is known to favor the formation of 1-carbethoxy-4-phenylthiosemicarbazide.[5]

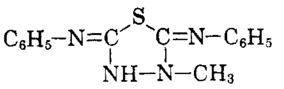
2,5-Dianilino-1,3,4-thiadiazole is reported to result as the reaction product of 4-phenylthiosemicarbazide and acetic acid,[6] concentrated sulfuric acid,[7] and sulfur monochloride,[8] or from 1,6-diphenylbithiourea with simple warming[9] or melting,[10] warming an ethanolic or acetic acid solution,[11] and with a variety of reagents such as concentrated hydrochloric acid,[12] phosgene in toluene,[13] acetyl chloride,[14] pyridine,[8] ferric chloride, iodine, phenylhydrazine, or 3% hydrogen peroxide in dilute sodium hydroxide solution[15] and acetic anhydride with subsequent hydrolysis of the acetyl groups.[16]

Guha and Sen[17] have reported that four different compounds could be isolated from the reaction mixture when 4-phenylthiosemicarbazide was heated with urea. One of them was formulated as 2-anilino-Δ^2-1,3,4-thiadiazoline-5-one (I, R = C_6H_5—) and was obtained also by Mistry and Guha,[18] who modified the above reaction by using amyl alcohol as a solvent. We repeated the experiment according to Mistry and Guha, but the compound (m.p. 246°), claimed by these authors to be 2-anilino-Δ^2-1,3,4-thiadiazoline-5-one (I, R = C_6H_5—), was identified as 2,5-dianilino-1,3,4-thiadiazole (III, R = C_6H_5—) on the basis of its analysis, mixed melting point and infrared spectrum (which revealed no typical carbonyl frequencies) and was identical with that of an authentic specimen synthesized from 1,6-diphenylbithiourea.

All other compounds obtained as the reaction products from the reaction of 4-substituted thiosemicarbazides with diethyl carbonate were identified as disubstituted 2,5-diamino-1,3,4-thiadiazoles (III) and in no case could a derivative of 1,3,4-thiadiazoline-5-one be obtained.



III



IV

The formation of the above-mentioned substances from substituted thiosemicarbazides can be explained by the intermediate formation of the corresponding isothiocyanates which then condense with unchanged thiosemicarbazides, giving rise to 1,6-disubstituted bithioureas. It was possible to isolate these bithioureas in some cases from the reaction mixture, and their conversion into derivatives of 1,3,4-thiadiazole is known to proceed easily. The intermediate formation of an isothiocyanate is

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[1] B. Stanovnik and M. Tišler, *J. Org. Chem.*, **25**, 2234 (1960).

[2] The structure of this and related compounds for which some tautomeric forms are possible[3] and which are proposed to exist in an equilibrium[4] will not be discussed here, although a close similarity of the ultraviolet spectra of III (R = C_6H_5—) and IV should favor the 1,3,4-thiadiazolidine structure.

[3] L. L. Bambas, *Five-membered Heterocyclic Compounds with Nitrogen and Sulfur or Nitrogen, Sulfur and Oxygen (except Thiazole)*, Interscience Publishers, Inc., New York, 1952, p. 124.

[4] R. Stolle and K. Fehrenbach, *J. prakt. Chem.*, **122**, 289 (1929).

[5] M. Tišler, *Arch. Pharm.*, **292**, 90 (1959).

[6] G. Pulvermacher, *Ber.*, **27**, 613 (1894).

[7] A. Silberg and I. Simiti, *Acad. rep. populare Romine, Filiala Cluj, Studii cercetări Stiint*, **10**, 313 (1959); *Chem. Abstr.*, **55**, 521 (1961).

[8] P. P. Patel and G. C. Chakravarti, *J. Indian Inst. Sci.*, A **13**, 85 (1930).

[9] P. C. Guha and D. R. Mehta, *J. Indian Inst. Sci.*, A **21**, 41 (1938); *Chem. Abstr.*, **33**, 598 (1939).

[10] M. Busch and W. Schmidt, *Ber.*, **46**, 2240 (1913).

[11] R. Walter and A. Stenz, *J. prakt. Chem.*, **74**, 222 (1906).

[12] S. L. Janniah and P. C. Guha, *J. Indian Inst. Sci.*, A **16**, 11 (1933).

[13] M. Freund and S. Wischewiansky, *Ber.*, **26**, 2877 (1893).

[14] E. Fromm, *Ann.*, **447**, 259 (1926).

[15] E. Fromm, *Ann.*, **433**, 1 (1923).

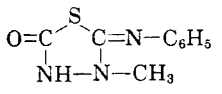
[16] P. C. Guha, *J. Am. Chem. Soc.*, **45**, 1036 (1923).

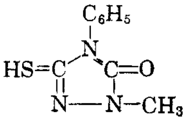
[17] P. C. Guha and P. C. Sen, *Quart. J. Indian Chem. Soc.*, **4**, 43 (1927).

[18] S. Mistry and P. C. Guha, *J. Indian Chem. Soc.*, **7**, 793 (1930).

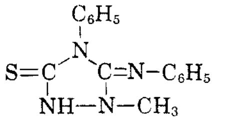
particularly substantiated in the case of 2-methyl-4-phenylthiosemicarbazide, where the compound IV is formed and not a 3,4-dimethyl derivative.

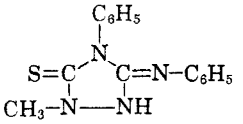
Compound IV was obtained also according to the procedure of Marckwald and Sedlaczek[19] when phosgene reacts with 2-methyl-4-phenylthiosemicarbazide in toluene. Both authors have reported, however, that they have obtained a substance (m.p. 163°) which they formulated as V and which on heating isomerized to VI (m.p. 212°).


V


VI

We were able to isolate from the reaction mixture only a 1,3,4-thiadiazole derivative (IV), as its hydrochloride, m.p. 262°, from which the free base, m.p. 175°, was isolated. This same substance was also isolated from the reaction mixture of 2-methyl-4-phenylthiosemicarbazide and phenylisothiocyanate (m.p. 175°) which Marckwald and Sedlaczek[19] formulated as VII or VIII.


VII


VIII

EXPERIMENTAL[20]

2,5-Dianilino-1,3,4-thiadiazole (III, R = C_6H_5—). A mixture of 1.67 g. (10 mmole) of 4-phenylthiosemicarbazide in 5 ml. of ethylene glycol monomethyl ether and 1.2 ml. (1.1 equivalent) of diethyl carbonate was refluxed on an oil bath for 4 hr. when some crystalline material separated. After cooling the reaction mixture, water was added and the precipitated crude material filtered. Recrystallization from aqueous ethanol gave almost colorless crystals with m.p. 247° (reported melting point for this erroneously formulated "2-anilino-Δ^2-1,3,4-thiadiazoline-5-one": 237°,[11] 240°,[6,7,10,13] 243°,[14,15] 246°,[17] 247°,[8,16] and 248°[9]). A mixed melting point with an authentic specimen obtained from 1,6-diphenylbithiourea with iodine[15] was undepressed, and the infrared spectra were identical and showed no carbonyl absorption. In ethanol λ_{max} 3150 Å, ϵ 21,470; yield, 20%.

Anal. Calcd. for $C_{14}H_{12}N_4S$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.29; H, 4.60; N, 20.83.

The same compound was obtained from 4-phenylthiosemicarbazide and urea in amyl alcohol according to the procedure of Mistry and Guha,[18] who formulated the substance as I (R = C_6H_5—). After five recrystallizations from ethanol the substance was obtained pure and showed no melting point depression with the above prepared authentic samples.

Acetylation of III (R = C_6H_5—) (100 mg.) with acetic anhydride (5 ml.) afforded the diacetyl product, m.p. 227° (recorded melting points are 213°,[17] 224°,[9,16] 225°,[8] and 227°[14]). In ethanol λ_{max} 2360 Å, ϵ 7950 and 2760 Å, ϵ 11,010.

Anal. Calcd. for $C_{18}H_{16}N_4O_2S$: N, 15.90. Found: N, 15.81 and 16.02.

Saponification of the diacetyl derivative with 2*N* hydrochloric acid (2 hr.) yielded the starting material with m.p. 247°.

Formation of 1,6-diphenylbithiourea. A. A mixture of 1.67 g. (10 mmole) of 4-phenylthiosemicarbazide, 5 ml. of ethylene glycol monomethyl ether, 1.2 ml. of diethyl carbonate and 0.5 ml. of concd. hydrochloric acid was refluxed on an oil bath for 1 hr. and from the resulting solution a precipitate slowly separated. The precipitate, collected after cooling, was recrystallized from aqueous ethanol and melted at 196°. The product was identical with an authentic specimen and with the product, obtained from 4-phenylthiosemicarbazide and ethyl chloroformate as in B.

B. A mixture of 1.67 g. (10 mmole) of 4-phenylthiosemicarbazide, 5 ml. of absolute ethanol and 1.2 equivalents of sodium ethoxide as 10% solution in ethanol was heated to boiling and to it was added, dropwise, 1.1 g. of ethyl chloroformate in 2 ml. of absolute ethanol. The mixture was then refluxed for 30 min., cooled to room temperature, and sodium chloride which separated was filtered. The filtrate was diluted with water and acidified with dilute hydrochloric acid. The precipitate which formed was filtered and washed with water until it was free of acid, and it was then recrystallized from aqueous ethanol (m.p. 196°, yield: 68%). The same procedure, in which the time of refluxing was 4-5 hr. afforded the cyclized product, *e.g.* III (R = C_6H_5—).

2,5-Diphenylimino-3-methyl-1,3,4-thiadiazolidine (IV). This substance was prepared according to the procedure of Marckwald and Sedlaczek[19] from 2-methyl-4-phenylthiosemicarbazide and phosgene; m.p. of the hydrochloride, 263°; m.p. of the base, 175° (lit.[19] gives m.p. 163°, but formulated the substance erroneously as V). The same compound was also obtained from 2-methyl-4-phenylthiosemicarbazide and phenylisothiocyanate (lit.[19] gives m.p. 175° and formulated it as VII or VIII). In addition the compound was prepared by heating a mixture of 1.81 g. (10 mmole) of 2-methyl-4-phenylthiosemicarbazide, 1.5 ml. of diethyl carbonate and 5 ml. of ethylene glycol monomethyl ether on an oil bath at 130° for 2 hr., diluting the cooled mixture with water, filtering the precipitate which formed, and recrystallizing it from aqueous ethanol; m.p. 175°, undepressed when admixed with the substance prepared as above; yield, 18%. In ethanol λ_{max} 2330 Å, ϵ 14,760 and 3080 Å, ϵ 16,220.

Anal. Calcd. for $C_{15}H_{14}N_4S$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.63; H, 5.04; N, 19.88.

If the reaction was carried out in the presence of hydrochloric acid (0.5 ml.), the same compound was isolated as hydrochloride, m.p. 263°.

2,5-Di-(p-ethoxyphenylamino)-1,3,4-thiadiazole (III, R = *p*-C_2H_5O—C_6H_4—) was prepared from the corresponding thiosemicarbazide and diethyl carbonate as described above, m.p. 213°.

Anal. Calcd. for $C_{18}H_{20}N_4O_2S$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.30; H, 5.55; N, 16.00.

An authentic specimen of this compound was obtained from 1,6-di-(*p*-ethoxyphenyl)bithiourea after refluxing for 30 min. with an aqueous iodine solution. The mixed melting point with the above compound was undepressed, and their infrared spectra were identical, showing no carbonyl frequencies; m.p. of 1,6-di-(*p*-ethoxyphenyl)bithiourea (from ethanol), 210°.

Anal. Calcd. for $C_{18}H_{22}N_4O_2S_2$: C, 55.38; H, 5.68; N, 14.35. Found: C, 55.31; H, 5.79. N, 14.42.

2,5-Di-(m-toluidino)-1,3,4-thiadiazole (III, R = *m*-CH_3—C_6H_4—) was prepared as above, m.p. 230° (from ethanol).

Anal. Calcd. for $C_{16}H_{16}N_4S$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.50; H, 5.16; N, 18.91.

An authentic sample of this compound with the same melting point was prepared from 1,6-di-(*m*-tolyl)bithiourea with an aqueous iodine solution as above; m.p. 177° (from ethanol).

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(19) W. Marckwald and E. Sedlaczek, *Ber.*, **29**, 2920 (1896).

(20) Melting points were determined on a Kofler block. Infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer with sodium chloride optics.

Anal. Calcd. for $C_{16}H_{18}N_4S_2$: C, 58.17; H, 5.49; N, 16.96. Found: C, 57.99; H, 5.62; N, 16.70.

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An Improved Procedure for the Dimetalation of Diphenyl Ether

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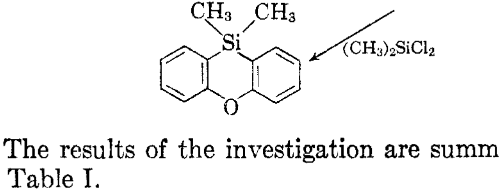
The dimetalation of diphenyl ether has been reported[1] to take place when two equivalents of *n*-butyllithium are refluxed with diphenyl ether for seventy-two hours. The position of dimetalation was established by carbonation of the dilithium intermediate to yield the known acid, 2,2′-dicarboxydiphenyl ether. Further proof was obtained by reaction of the 2,2′-dilithiodiphenyl ether with R_2SiX_2 reagents to obtain the appropriate cyclic silicon compounds.[1,2]

The long reaction time (seventy-two hours) and the low yield of product (25.1%) prompted the development of some modifications in the dimetalation procedure. The reaction was reinvestigated both in regard to the organometallic reagent and to the solvent system. Derivatization was carried out through the use of dichlorodimethylsilane to obtain the cyclic silicon compound, 10,10-dimethylphenoxasilin.[1]



The results of the investigation are summarized in Table I.

In had been shown previously that, in almost every metalation reaction, the use of tetrahydrofuran gave significantly higher yields of metalated product compared to those obtained in diethyl ether.[3] The present investigation also indicated the much greater activating effect of tetrahydrofuran in metalation reactions. Diphenyl ether was dimetalated quite rapidly by *n*-butyllithium in this solvent, and in a mixed tetrahydrofuran-ether solvent system. The reaction in the mixed solvent system actually gave a greater yield of derivative (50.5%) than when carried out in tetrahydrofuran alone (16.6%). Phenyllithium in the mixed solvent system was also sufficiently reactive to effect dimetalation, but to a lesser extent (23.7%) than *n*-butyllithium. Methyllithium in tetrahydrofuran did not give a derivative indicative of dimetalation.

The use of a mixed solvent system increased the stability of the organolithium reagents. Whereas *n*-butyllithium in tetrahydrofuran alone is very unstable even at room temperature,[4] the use of mixed tetrahydrofuran ether solvent allowed the reaction to be run either at room temperature or at a mild reflux.

The optimum conditions for the dimetalation of diphenyl ether finally developed involved the preparation of *n*-butyllithium (1*N*) in diethyl ether, followed by addition to a tetrahydrofuran solution of diphenyl ether. The final solvent ratio of ether to tetrahydrofuran was about 1.3:1 for a maximum yield at a reasonable reaction time. The reaction mixture can be warmed mildly for five hours before use to obtain a maximum yield (50.5%), or it can be stirred at room temperature for fourteen hours. The latter choice gave a lower yield of derivative (32.0%), but proved convenient because the reaction mixture could be stirred overnight before subsequent reaction. The former choice required closer attention.

The only limiting factor in the dimetalation appears to be a lower yield due to handling difficulties when large quantities of reagents are employed. Notwithstanding, the procedure appears to improve greatly over the seventy-two hours of refluxing used previously to obtain a 25.1% yield of product.

EXPERIMENTAL[5]

Dimetalation of diphenyl ether by n-butyllithium in tetrahydrofuran-ether mixed solvent (1:1) *at room temperature.* To a solution of 25.5 g. (0.15 mole) of diphenyl ether and 250 ml. of tetrahydrofuran was added slowly 0.35 mole of *n*-butyllithium in 290 ml. of ether solution. The reaction flask was cooled at ice-bath temperature throughout the addition, which was completed in 25 min. The ice bath was removed and stirring was continued. The dark green reaction mixture gave a strongly positive Color Test II.[6] Six hours later, Color Test II gave an initial negative test, but a dark reddish brown color developed upon standing. Eight hours later the same results were obtained, and it was concluded that this was a

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[1] K. Oita and H. Gilman, *J. Am. Chem. Soc.*, **79**, 339 (1957).

[2] H. Gilman and D. Miles, *J. Org. Chem.*, **23**, 1363 (1958).

[3] (a) H. Gilman and R. D. Gorsich, *J. Org. Chem.*, **22**, 687 (1957). (b) D. W. Mayo, P. D. Shaw, and M. Rausch, *Chem. and Ind.* (*London*), 1388 (1957). (c) H. Gilman and S. Gray, *J. Org. Chem.*, **23**, 1476 (1958). (d) P. Tomboulian, *J. Org. Chem.*, **24**, 229 (1959).

[4] H. Gilman and B. J. Gaj, *J. Org. Chem.*, **22**, 1165 (1957).

[5] All melting points are uncorrected. Reactions were carried out under an atmosphere of dry, oxygen-free nitrogen. Tetrahydrofuran was freed from peroxides and moisture before use by refluxing over sodium, followed by distillation from lithium aluminum hydride.

[6] H. Gilman and J. Swiss, *J. Am. Chem. Soc.*, **60**, 1847 (1940).